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(54) Title: HUMAN INTERFERON TAU COMPOSITIONS AND METHODS OF USE

(57) Abstract

The present invention describes the isolation and characterization of multiple forms of human interferon-τ. Protein and nucleic acid coding sequences for the multiple forms are disclosed. In further aspects, the invention relates to methods of producing and using human interferon-τ molecules.

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HUMAN INTERFERON TAU COMPOSITIONS AND METHODS OF USE

Field of the Invention

The present invention relates to human interferon-τ compositions and methods of use.

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Background of the Invention

Conceptus membranes, or trophectoderm, of various mammals produce biochemical signals that allow for the establishment and maintenance of pregnancy (Bazer, *et al.*, 1983). One such protein, ovine trophoblast protein-one (oTP-1), was identified as a low molecular weight protein secreted by sheep conceptuses between days 10 and 21 of pregnancy (Wilson, *et al.*; Bazer, *et al.*, 1986). The protein oTP-1 was shown to inhibit uterine secretion of prostaglandin F_2-alpha, which causes the corpus luteum on the ovary to undergo physiological and endocrinological demise in nonpregnant sheep (Bazer, *et al.*, 1986). Accordingly, oTP-1 has antiluteolytic biological activity. The primary role of oTP-1 was assumed to be associated with the establishment of pregnancy.

oTP-1 was subsequently found to (i) exhibit limited homology (50-70%) with interferon alphas (IFNα) of various species (Imakawa, *et al.*), and (ii) bind to a Type I interferon receptor (Stewart, *et al.*). Despite some similarities with IFNα, oTP-1 has several features that distinguish it from IFNα including the following: oTP-1's role in reproductive biochemistry (other interferons are not known to have any role in the biochemical regulation of reproductive cycles), oTP-1's cellular source -- trophoblast cells (IFNα is derived from lymphocytes cells), oTP-1's size -- 172 amino acids (IFNα is typically about 166 amino acids), and oTP-1 is weakly inducible by viruses (IFNα is highly inducible by viruses). The International Interferon Society recognizes oTP-1 as belonging to an entirely new class of interferons which have been named interferon-tau (IFNτ). The Greek letter τ stands for trophoblast.

The interferons have been classified into two distinct groups: type I interferons, including IFNα, IFNβ, and IFNω (also known as IFNαII); and type II interferons, represented by IFNγ (reviewed by DeMaeyer, *et al.*). In humans, it is estimated that there are at least 17 IFNα non-allelic genes, at least about 2 or 3 IFNβ non-allelic genes, and a single IFNγ gene.

IFNα's has been shown to inhibit various types of cellular proliferation. IFNα's are especially useful against hematologic malignancies such as hairy-cell leukemia (Quesada, *et al.*). Further, these proteins have also shown activity against multiple myeloma, chronic lymphocytic leukemia, low-grade lymphoma, Kaposi's sarcoma, chronic myelogenous leukemia, renal-cell carcinoma, urinary bladder tumors and ovarian cancers (Bonnem, *et al.*; Oldham). The role of interferons and interferon receptors in the pathogenesis of certain autoimmune and inflammatory diseases has also been investigated (Benoit, *et al.*).

IFNα's are also useful against various types of viral infections (Finter, *et al.*). Alpha interferons have shown activity against human papillomavirus infection, Hepatitis B, and Hepatitis C infections (Finter, *et al.*; Kashima, *et al.*; Dusheiko, *et al.*; Davis, *et al.*).

Significantly, however, the usefulness of IFNα's has been limited by their toxicity: use of interferons in the treatment of cancer and viral disease has resulted in serious side effects, such as fever, chills, anorexia, weight loss, and fatigue (Pontzer, *et al.*, 1988; Oldham). These side effects often require (i) the interferon dosage to be reduced to levels that limit the effectiveness of treatment, or (ii) the removal of the patient from treatment. Such toxicity has reduced the usefulness of these potent antiviral and antiproliferative proteins in the treatment of debilitating human and animal diseases.

A recent PCT International Application (WO 94/10313, published 11 May 1994) described the production of interferon-τ proteins. The antiviral and anticellular proliferation properties of these proteins and polypeptides were also described. The disclosure discussed ovine interferon-τ and an isolate of human interferon-τ.

Summary of the Invention

The present invention relates to compositions of and methods employing human interferon-τ's. In one embodiment, the invention includes an isolated nucleic acid molecule that encodes a human interferon-τ. Several variants of human interferon-τ (HuIFNτ) are disclosed herein, including HuIFNτ1, HuIFNτ2, HuIFNτ3, HuIFNτ4, HuIFNτ5, HuIFNτ6 and HuIFNτ7. The nucleic acid molecules of the present invention include nucleic acid molecules having the following sequences: SEQ ID NO:29, SEQ ID NO:15, SEQ ID NO:11, SEQ ID NO:19, SEQ ID NO:13, SEQ ID NO:7 and SEQ ID NO:9.

The nucleic acids of the present invention may further include sequences encoding leader sequences for the human interferon-τ which they encode, for example, SEQ ID NO:27 or SEQ ID NO:28.

The nucleic acid molecules described above encode human interferon-τ proteins and polypeptides of the present invention. The amino acid sequence of a human interferon-τ protein is typically a variant sequence of the human interferon-τ core sequence (HuIFNτCS; SEQ ID NO:34). It will be understood, however, that variants of the core sequence can be modified by introducing conservative amino acid substitutions that do not significantly change the activity or characteristics of the modified variant with respect to the corresponding unmodified variant. Such modified variants are also included within the scope of the present invention. In a preferred embodiment, such modified variants of the present invention do not include modifications at positions 84 and 85 of a mature interferon-τ amino acid sequence.

In one general embodiment the HuIFNτ proteins or polypeptides are "Group I" proteins or polypeptides, derived from the core sequence represented as SEQ ID NO:31. Examples include HuIFNτ1 (SEQ ID NO:30) and HuIFNτ2 (SEQ ID NO:16). In another general embodiment they are "Group II" proteins or polypeptides, derived from the core sequence represented as SEQ ID NO:32 and exemplified by HuIFNτ3 (SEQ ID NO:20), HuIFNτ4 (SEQ ID NO:12) and HuIFNτ5 (SEQ ID NO:14). In still another general embodiment they are "Group III" proteins or polypeptides, derived from the core sequence represented as SEQ ID NO:33, with examples including HuIFNτ6 (SEQ ID NO:8) and HuIFNτ7 (SEQ ID NO:10).

A second aspect of the invention includes an expression vector having a nucleic acid containing an open reading frame that encodes a human interferon-τ, including the nucleic acid and polypeptide sequences described above. The vector further includes regulatory sequences effective to express said open reading frame in a host cell. The regulatory sequence may include sequences useful for targeting or secretion of the human IFNτ polypeptide: such sequences may be endogenous (such as the normally occurring human IFNτ leader sequences, present, for example, in SEQ ID NO:27) or heterologous (such as a secretory signal recognized in yeast, mammalian cell, insect cell, tissue culture or bacterial expression systems). In the expression vector, regulatory sequences may also include, 5' to said nucleic acid sequence, a promoter region and an ATG start codon in-frame with the human interferon-τ coding sequence, and 3' to said coding sequence, a translation termination signal followed by a transcription termination signal.

In a further embodiment, the invention includes a method of recombinantly producing human interferon-τ. In the method, the expression vector, containing sequences encoding a

human interferon-τ open reading frame (ORF), is introduced into suitable host cells, where the vector is designed to express the ORF in the host cells. The transformed host cells are then cultured under conditions that result in the expression of the ORF sequence. Numerous vectors and their corresponding hosts are useful in the practice of this method of the invention, including, lambda gt11 phage vector and *E. coli* cells. Other host cells include, yeast, mammalian cell, insect cell, tissue culture, plant cell culture, transgenic plants or bacterial expression systems.

In another embodiment, the invention includes an isolated human interferon-τ protein or polypeptide. The protein may be recombinantly produced. Further, the protein or polypeptide may include any of the following human interferon-τ sequences: SEQ ID NO:30, SEQ ID NO:16, SEQ ID NO:20, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:8, and SEQ ID NO:10.

The invention further includes a method of inhibiting tumor cell growth. In the method, the tumor cells are contacted with a human τ-interferon polypeptide at a concentration effective to inhibit growth of the tumor cells. The human interferon-τ may be a part of any acceptable pharmacological formulation. Tumor cells whose growth may be inhibited by human interferon-τ include, but are not limited to, human carcinoma cells, hematopoietic cancer cells, human leukemia cells, human lymphoma cells, and human melanoma cells. In one embodiment, the tumor cells are steroid-sensitive tumor cells, for example, mammary tumor cells.

In yet another embodiment of the present invention, human interferon-τ polypeptides are used in a method of inhibiting viral replication. In this method, cells infected with a virus are contacted with human τ-interferon at a concentration effective to inhibit viral replication within said cells. The human interferon-τ may be a part of any acceptable pharmacological formulation. The replication of both RNA and DNA viruses may be inhibited by human interferon-τ polypeptides. Exemplary RNA viruses include human immunodeficiency virus (HIV) or hepatitis c virus (HCV). An exemplary DNA virus is hepatitis B virus (HBV).

In yet another aspect, the present invention includes a method of enhancing fertility in a female mammal. In this method, an effective mammalian fertility enhancing amount of human interferon-τ is administered to the female mammal in a pharmaceutically acceptable carrier.

The invention also includes isolated human interferon-τ polypeptides. These polypeptides are derived from the human interferon-τ amino acid coding sequence and are

typically between about 20 and 172 amino acids in length, preferably between about 85 and 172 amino acids in length.

Also included in the invention is a fusion polypeptide that contains a human interferon-τ polypeptide that is between 8 and 172 amino acids long and derived from a human interferon-τ amino acid coding sequence, and a second soluble polypeptide.

In one embodiment, human interferon-τ sequences are used in hybrid fusion constructs with other type I interferons to reduce the toxicity of the other type I interferons (*e.g.*, interferon-α and interferon-β). Experiments performed in support of the present invention suggests that the portion of an alpha or beta interferon molecule responsible for the increased cytotoxicity of those molecules with respect to that of interferon tau resides in the first about 8 - 37 amino acids. Accordingly, the DNA encoding such a reduced-cytotoxicity hybrid molecule is formed of a 5' end segment that encodes the N-terminal amino acid sequence of an interferon-tau polypeptide, and a 3' end segment that encodes the C-terminal amino acid sequence of a non-tau interferon type I polypeptide. The two segments are spliced in a region corresponding to the portion of a mature interferon polypeptide between about amino acid residues 8 and 37. In one embodiment, the 5' end segment further includes a leader sequence. Such hybrid construct may be used to confer, *e.g.*, the antiviral activity of an IFNα with the reduced cytotoxicity of an IFNτ. In a broader context, such compositions may be used to reduce the toxicity of the other types of interferons when the interferons are used in pharmaceutical formulations or in therapeutic applications.

Examples of sequences encoded by the 5' end segment include variants derived from the first 8 to 37 residues of SEQ ID NO:34, such as the first 8 to 37 residues of a sequence selected from the group consisting of SEQ ID NO:16, SEQ ID NO:20, and SEQ ID NO:30.

The 3' end segment may encode, in various embodiments, an amino acid sequence derived from an interferon alpha 1, alpha 2, beta or omega. The 3' end segment may also encode a consensus sequence from any of the above. Preferred embodiments are where the sequence is derived from a human source, such as a human IFNα or human IFNβ. An exemplary human IFNα sequence (HUMIFNN) suitable for the construction of a reduced-toxicity hybrid molecule can be obtained from GenBank under accession number M28585.

In a general embodiment, the two segments are spliced in a region corresponding to the portion of a mature interferon polypeptide between about residues 8 and 28. In another general embodiment, the two segments are spliced in a region corresponding to the portion of a mature interferon polypeptide between about residues 8 and 22. In yet another general

embodiment, the two segments are spliced in a region corresponding to the portion of a mature interferon polypeptide between about residues 8 and 16.

The invention also includes purified antibodies that are immunoreactive with human interferon-τ. The antibodies may be polyclonal or monoclonal.

These and other objects and features of the invention will be more fully appreciated when the following detailed description of the invention is read in conjunction with the accompanying drawings.

Brief Description of the Figures

Figure 1 presents the complete nucleic acid and amino acid sequence of an OvIFNτ sequence.

Figure 2 shows a comparison of the predicted protein sequences of a human interferon-τ gene and an ovine interferon-τ gene. Divergent amino acids are indicated by presentation of the alternative amino acid on the line below the nucleic acid sequences.

Figures 3A and 3B present an alignment of nucleic acid sequences encoding IFNτ polypeptides.

Figures 4A and 4B present an alignment of amino acid sequences of IFNτ polypeptides.

Detailed Description of the Invention

I. Definitions

Human Interferon-τ (HuIFNτ) refers to any one of a family of interferon proteins that contains (i) a variant sequence of the human interferon-τ core sequence (HuIFNτCS; SEQ ID NO:34), or (ii) a sequence corresponding to a particular variant of HuIFNτCS (SEQ ID NO:34) and containing conservative amino acid substitutions, where the substitutions do not significantly change the activity or characteristics of that particular variant. Examples of HuIFNτ variant amino acid sequences include HuIFNτ sequences represented herein by HuIFNτ1 (SEQ ID NO:30), HuIFNτ2 (SEQ ID NO:16), HuIFNτ3 (SEQ ID NO:20), HuIFNτ4 (SEQ ID NO:12), HuIFNτ5 (SEQ ID NO:14), HuIFNτ6 (SEQ ID NO:8) and HuIFNτ7 (SEQ ID NO:10). Activities and characteristics associated with HuIFNτ include at least one, preferably two or more, from the following group of characteristics: (a) expressed during embryonic development stages, (b) anti-luteolytic properties, (c) anti-viral properties, and (d) anti-cellular proliferation properties.

A *human interferon-τ polypeptide* is a polypeptide having between about 20 and 172 amino acids, preferably between about 85 and 172 amino acids, derived from a mature human interferon-τ amino acid coding sequence, where said 20 to 172 or 85 to 172 amino acids are contiguous in native interferon-τ. Such contiguous amino acid regions can also be assembled into polypeptides where two or more such interferon-τ regions are joined that are normally discontinuous in the native protein.

A *mature interferon-τ polypeptide* is a full-length interferon-τ polypeptide less the leader sequence. A mature human interferon-τ polypeptide typically contains between about 171 and 172 amino acid residues.

A *core sequence* is sequence having at least one variable position represented by two or more individual amino acid residues. In an amino acid core sequence, such a variable position is indicated as "Xaa". Each core sequence defines two or more *variant sequences*, or *variants*, having a single amino acid residue at each position. For example, the core sequence "Ser Xaa Phe", where Xaa is Leu or Ile, defines the variant sequences "Ser Leu Phe" and "Ser Ile Phe".

Conservative amino acid substitutions are substitutions which do not result in a significant change in the activity (*e.g.*, antiviral activity) or tertiary structure of a selected polypeptide. Such substitutions typically involve replacing a selected amino acid residue with a different residue having similar physico-chemical properties. For example, substitution of Glu for Asp is considered a conservative substitution since both are similarly-sized negatively-charged amino acids. Groupings of amino acids by physico-chemical properties are known to those of skill in the art and can be found, for example, in Schulz and Schirmer (1979).

When a first polypeptide fragment is said to *correspond* to a second polypeptide fragment, it means that the fragments or regions thereof are essentially co-extensive with one another when the sequences representing the fragments are aligned using a sequence alignment program, such as "MACVECTOR" (IBI, New Haven, CT). *Corresponding* polypeptide fragments typically contain a similar, if not identical, number of residues. It will be understood, however, that corresponding fragments may contain insertions or deletions of residues with respect to one another, as well as some differences in their sequences.

A polypeptide sequence or fragment is *derived* from another polypeptide sequence or fragment when it has the same sequence of amino acid residues as the corresponding region of the fragment from which it is derived. A variant or variant sequence derived from a core sequence contains one of the sequences defined by the core sequence.

II. Ovine and Bovine Interferon-τ Genes

Ovine interferon-τ (OvIFNτ) is a major conceptus secretory protein produced by the embryonic trophectoderm during the critical period of maternal recognition in sheep. The isolation of OvIFNτ protein has been described (Godkin, *et al.*; Vallet, *et al.*. 1987, 1988). One isolate of mature OvIFNτ is 172 amino acids in length (SEQ ID NO:2; exemplary nucleic acid coding sequence, SEQ ID NO:1). The cDNA coding sequence contains an additional 23 amino acids at the amino-terminal end of the mature protein (Imakawa, *et al.*, 1987). The coding sequence of this OvIFNτ isolate is presented as Figure 1.

Relative to other interferons, OvIFNτ shares the greatest sequence similarity with the interferonωs (IFNωs).

A homologous protein to OvIFNτ was isolated from cows (bIFNτ; Helmer, *et al.*; Imakawa, *et al.*, 1989). OvIFNτ and BoIFNτ (i) have similar functions in maternal recognition of pregnancy, and (ii) share a high degree of amino acid and nucleotide sequence homology between mature proteins. The nucleic acid sequence homology between OvIFNτ and BoIFNτ is 76.3% for the 5' non-coding region, 89.7% for the coding region, and 91.9% for the 3' non-coding region. The amino acid sequence homology is 80.4%.

III. Isolation and Characterization of Human Interferon-τ Genes

A. Identification and Cloning of Human Genomic Sequences Encoding Interferon-τ Protein

Human DNA was screened for sequences homologous to interferon-τ (Example 1). Several sequences that hybridized with the OvIFNτ cDNA probe were identified. Several clones containing partial sequences of human interferon-τ were then isolated (Example 2). Two synthetic 25-mer oligonucleotides, corresponding to sequences from the OvIFNτ cDNA (Imakawa, *et al.*, 1987) were synthesized. These primers were employed in amplification reactions using DNA derived from the following two cDNA libraries: human term placenta and human term cytotrophoblast. The resulting amplified DNA fragments were electrophoretically separated and a band containing human IFNτ (HuIFNτ) amplification products was isolated. The amplification products were subcloned and the inserted amplification products sequenced using the dideoxy termination method.

Comparison of sequences from five of these clones revealed a high degree of sequence homology between the isolates, but the sequences were not identical. This result suggests the existence of multiple variants of human interferon-τ genes. Analysis of the nucleotide and protein sequences suggests that human interferon-τ genes may be classified on the basis of sequence homology into at least three groups. The groups are presented below.

Example 3 describes the isolation of several full-length human IFNτ genes. High molecular weight DNA was isolated from peripheral blood mononuclear cells (PBMCs) and size-fractionated. Fractions were tested for the presence of HuIFNτ sequences using polymerase chain reaction: DNA molecules from fractions that tested amplification positive were used to generate a subgenomic library in λgt11.

This subgenomic library was plated and hybridized with an OvIFNτ cDNA probe (Example 3A). Approximately 20 clones were identified that hybridized to the probe. Plaques corresponding to the positive clones were passaged, DNA isolated and analyzed by amplification reactions using OvIFNτ primers. Of these twenty plaques, six plaques generated positive PCR signals. The phage from these six clones were purified and the inserts sequenced. One of the inserts from one of these six clones was used as a hybridization probe in the following screening.

Recombinant phage from the λgt11 subgenomic library were screened using the human DNA hybridization probe just described (Example 3B). Five clones giving positive hybridization signals were isolated and the inserts sequenced. The sequences from three of the clones overlapped, and the resulting consensus nucleic acid sequence (HuIFNτ1) is presented as SEQ ID NO:3 with the predicted protein coding sequence presented as SEQ ID NO:4 (containing the leader sequence). The predicted mature protein coding sequence is presented as SEQ ID NO:30.

The sequences from the other two clones are presented as SEQ ID NO:15 (HuIFNτ2) and SEQ ID NO:17 (HuIFNτ3). The predicted mature amino acid sequence from HuIFNτ2 is presented as SEQ ID NO:16. The predicted amino acid sequence from HuIFNτ3 is presented as SEQ ID NO:18, and the mature amino acid sequence as SEQ ID NO:20.

For expression of recombinant HuIFNτ, a coding sequence can be placed in a number of bacterial expression vectors: for example, lambda gt11 (Promega, Madison WI); pGEX (Smith, *et al.*, 1988); pGEMEX (Promega); and pBS (Stratagene, La Jolla CA) vectors. Other bacterial expression vectors containing suitable promoters, such as the T7 RNA polymerase promoter or the *tac* promoter, may also be used.

Yeast vectors can also be used in the practice of the present invention. They include 2 microns plasmid vectors (Ludwig, *et al.*), yeast integrating plasmids (YIps; *e.g.*, Shaw, *et al.*), YEP vectors (Shen, *et al.*), yeast centromere plasmids (YCps; *e.g.*, Ernst), and the like. Preferably, the vectors include an expression cassette containing an effective yeast promoter, such as the MFα1 promoter (Ernst; Bayne, *et al.*), GADPH promoter (glyceraldehyde-3-phosphate-dehydrogenase; Wu, *et al.*), the galactose-inducible GAL10 promoter (Ludwig, *et*

al.; Feher, *et al.*; Shen, *et al.*), or the methanol-regulated alcohol oxidase (EWES) promoter. The EWES promoter is particularly useful in *Pocket pastoris* host cells (for example, the EWES promoter is used in pHIL and pPIC vectors included in the *Pocket* expression kit, available from Invitrogen, San Diego, CA).

The expression cassette may include additional elements to facilitate expression and purification of the recombinant protein, and/or to facilitate the insertion of the cassette into a vector or a yeast chromosome. For example, the cassette may include a signal sequence to direct secretion of the protein. An exemplary signal sequence suitable for use in a variety of yeast expression vectors is the MFα1 pre-pro signal sequence (Bayne, *et al.*; Ludwig, *et al.*; Shaw, *et al.*). Other signal sequences may also be used. For example, the Pho1 signal sequence (Elliot, *et al.*) is particularly effective in *Pocket Pastoris* and *Schizosaccharomyces pombe* host cells.

Exemplary expression cassettes include (i) a cassette containing (5' to 3') the EWES promoter, the Pho1 signal sequence, and a DNA sequence encoding HuIFNτ, for expression in *P. pastoris* host cells, and (ii) a cassette containing (5' to 3') the MFα1 promoter, the MFα1 pre-pro signal sequence, and a DNA sequence encoding mature HuIFNτ, for expression in *S. cerevisiae* host cells.

Additional yeast vectors suitable for use with the present invention include, but are not limited to, other vectors with regulatable expression (Hitzeman, *et al.*; Rutter, *et al.*; Oeda, *et al.*). The yeast transformation host is typically *Saccharomyces cerevisiae*, however, as illustrated above, other yeast suitable for transformation can be used as well (*e.g.*, *Schizosaccharomyces pombe*, *Pocket pastoris* and the like).

The DNA encoding the HuIFNτ polypeptide can be cloned into any number of commercially available vectors to generate expression of the polypeptide in the appropriate host system. These systems include the above described bacterial and yeast expression systems as well as the following: baculovirus expression (Reilly, *et al.*;-Beames, *et al.*; Clontech, Palo Alto CA); plant cell expression, transgenic plant expression (*e.g.*, Gelvin and Schilperoot), and expression in mammalian cells (Clontech, Palo Alto CA; Gibco-BRL, Gaithersburg MD).

The recombinantly produced polypeptides can be expressed as fusion proteins or as native proteins. The recombinantly produced polypeptides are typically isolated from lysed cells or culture media. The protein can be further purified after expression by standard methods, including size fractionation (column chromatography or preoperative gel electrophoresis) or affinity chromatography (using, for example, anti-HuIFNτ antibodies (solid

support available from Pharmacia, Piscataway NJ). Protein preparations can also be concentrated by, for example, filtration (Amicon, Danvers, Mass.).

Recombinant HuIFNτ obtained by such methods exhibits antiviral activity. Further, one advantage of HuIFNτ over other interferons (*e.g.*, IFNα) is that treatment of a subject with therapeutic doses of HuIFNτ does not appear to be associated with cytotoxicity.

B. HuIFNτ Sequence Comparisons and Localization Studies

Comparison of the predicted protein sequences (Figure 2) of one of the human interferon-τ genes (SEQ ID NO:30) and the ovine interferon-τ gene demonstrates the levels of sequence homology and divergence at the amino acid level.

An alignment of the nucleic acid sequences of the seven human interferon-τ nucleic acid sequences, described herein (Examples 2 and 3), with ovine interferon-τ is shown in Figures 3A and 3B. Sequences of OvIFNτ (oIFNt), HuIFNτ1, HuIFNτ2, and HuIFNτ3 start at the upper left corner of Figure 3A with the initiation ATG codon and continue through the second page of the figure. Sequences of HuIFNτ4, HuIFNτ5, HuIFNτ6 and HuIFNτ7 start approximately half-way down Figure 3A with the CAG codon at amino acid position 40 (to the right of the exclamation marks) and continue through the second page of the figure. The 5' and 3' ends of each of the clones for HuIFNτ4, HuIFNτ5, HuIFNτ6 and HuIFNτ7 are represented by exclamation marks.

The complete coding sequence of OvIFNτ is presented in the top row of each aligned set. Nucleotides in the other sequences are indicated only at positions where they differ from those of OvIFNτ. Lower case letters represent nucleotide changes that do not result in amino acid changes, while upper case letters represent those changes that result in an amino acid substitution.

An alignment of the seven corresponding amino acid sequences, constructed in essentially the same manner as described above, is presented in Figures 4A and 4B. As above, the complete amino acid sequence of OvIFNτ is presented in the top row, and amino acids of other sequences are indicated only at positions where they differ from the ovine sequence.

An examination of the alignments reveals that the seven sequences may be grouped into at least three groups. Group I contains HuIFNτ1 and HuIFNτ2, group II contains HuIFNτ3, HuIFNτ4 and HuIFNτ5, and group III contains HuIFNτ6 and HuIFNτ7. These groups may represent families of interferon-t genes having distinct cellular functions. The core polypeptide sequences defining the groups are presented herein as SEQ ID NO:31, SEQ ID NO:32 and

SEQ ID NO:33, respectively. A general core HuIFNτ amino acid sequence is presented herein as SEQ ID NO:34.

These groupings were established based on the following criteria. In mature proteins, Group I HuIFNτs have an asparagine (ASN) at amino acid position number 95 (numbers in reference to Figures 4A to 4B), a methionine (MET) at amino acid position number 104, and a leucine (LEU) at amino acid position number 120; Group II HuIFNτs have an aspartic acid (ASP) at amino acid position number 95, a threonine (THR) at amino acid position number 104, and a methionine (MET) at amino acid position number 120; and Group III HuIFNτs have an arginine (ARG) at amino acid position number 72, a valine (VAL) at amino acid position number 120, and a serine (SER) at amino acid position number 122.

The nucleic acid and polypeptide human IFNτ sequences presented as SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, and SEQ ID NO:20 can be used as the source for specific primers and probes to detect isolates of further human IFNτ coding sequences and/or pseudogenes. Further, as described above, there may be more than one isoform of the HuIFNτ protein and more than one coding sequence per species. The specific nucleic acid probes used in the practice of the present invention and antibodies reactive with the HuIFNτ polypeptides of the present invention may be useful to isolate unidentified variants of interferon-τ in mammals, according to the methods of the invention disclosed herein (*e.g.*, Examples 1 and 2).

The presence of HuIFNτ mRNA in human term placenta and amniocytes was analyzed. Results from these studies suggested that the presence of human IFNτ mRNA in the feto-placental annex. The aminocytes also expressed the messages corresponding to OvIFNτ primers and a HuIFNτ probe, suggesting that the expression of HuIFNτ mRNA is not limited to the term placenta.

In addition, a RT-PCR analysis for the presence of HuIFNτ was applied to the total cellular RNA isolated from human adult lymphocytes: the results demonstrated that HuIFNτ mRNA exists in lymphocytes.

The expression of interferon-τ in human tissue was also examined using *in situ* hybridization; specific hybridization was observed in all term and first trimester placental tissues.

First trimester placental villi (composed of an outer layer of syncytiotrophoblast, an underlying layer of cytotrophoblast, and a central stromal region with various types of

mesenchymal cells) displayed the highest transcript level of HuIFNτ in the cytotrophoblast cells. Less intense but detectable levels were present in both the syncytiotrophoblast and stromal cells. A similar pattern of transcript expression was demonstrated in the placental villi of term tissue but the level of signal detection was low. First trimester extravillous trophoblasts displayed the highest amount of message and stained positive when present in the maternal blood spaces.

Howatson, *et al.*, noted IFNα production in the syncytiotrophoblast of chorionic villi in both first trimester and term tissues. Also, Paulesu, *et al.* observed IFNα in extravillous trophoblast as well as syncytiotrophoblasts, noting more intense and abundant reactivity in first trimester placental tissue when compared to those taken at term. These investigators employed antibodies raised against human IFNα subtypes, and none observed any IFNα in the villous cytotrophoblasts.

The human IFNτ gene appears to be highly expressed in early placental tissues (*e.g.*, first trimester placenta) by migrating extravillous trophoblasts, but is also expressed in villous syncytiotrophoblasts, villous cytotrophoblasts, and various stromal cells.

IV. Human Interferon-τ Polypeptide Fragments and Protein Modifications

A. HuIFNτ Polypeptide Fragments

Portions of the HuIFNτ interferon molecule may be used to substitute regions of other interferon molecules. For example, the region of an interferon alpha molecule that is responsible for increased cytotoxicity, relative to HuIFNτ treatment, can be identified by substituting polypeptide regions derived from HuIFNτ for regions of an interferon alpha molecule. Such substitutions can be carried out by manipulation of synthetic genes (see below) encoding the selected HuIFNτ and interferon alpha molecules, coupled to the functional assays, such as, antiviral, antiproliferative and cytotoxicity assays (*e.g.*, WO 94/10313, published 11 May 1994). Exemplary HuIFNτ polypeptide fragments include, but are not limited to, the polypeptides presented as SEQ ID NO:21 to SEQ ID NO:26.

Synthetic gene constructs facilitate introduction of mutations for possible enhancement of antitumor (anticellular proliferative) and antiviral activities. Further, the disparate regions of the molecule responsible for different functions allows for separate manipulation of different functions.

Synthetic peptides can be generated which correspond to the HuIFNτ polypeptides of the present invention. Synthetic peptides can be commercially synthesized or prepared using standard methods and apparatus in the art (Applied Biosystems, Foster City CA).

Alternatively, oligonucleotide sequences encoding peptides can be either synthesized directly by standard methods of oligonucleotide synthesis, or, in the case of large coding sequences, synthesized by a series of cloning steps involving a tandem array of multiple oligonucleotide fragments corresponding to the coding sequence (Crea; Yoshio *et al.*; Eaton *et al.*). Oligonucleotide coding sequences can be expressed by standard recombinant procedures (Maniatis *et al.*; Ausubel, *et al.*).

The biological activities of the interferon-τ polypeptides described above can be exploited using either the human interferon-τ polypeptides alone or conjugated with other proteins (see below).

B. Production of Fusion Proteins

In another aspect, the present invention includes human interferon-τ or human interferon-τ-derived polypeptides covalently attached to a second polypeptide to form a fused, or hybrid, protein. The human interferon-τ sequences making up such fused proteins can be recombinantly-produced-interferon-τ or a bioactive portion thereof, as described above.

For example, where human interferon-τ is used to inhibit viral expression, polypeptides derived from HuIFNτ demonstrating antiviral activity may be advantageously fused with a soluble peptide, such as, serum albumin, an antibody (*e.g.*, specific against an virus-specific cell surface antigen), or an interferon alpha polypeptide.

In one embodiment, the HuIFNτ polypeptides provide a method of reducing the toxicity of other interferon molecules (*e.g.*, IFNβ or IFNα) by replacing toxicity-associated regions of such interferons with, for example, corresponding interferon-τ regions having lower toxicity.

In another embodiment, fusion proteins are generated containing human interferon-τ regions that have anticellular proliferation properties. Such regions may be obtained from, for example, the human interferon-τ sequences disclosed herein.

The fused proteins of the present invention may be formed by chemical conjugation or by recombinant techniques. In the former method, the human interferon-τ and second selected polypeptide are modified by conventional coupling agents for covalent attachment. In one exemplary method for coupling soluble serum albumin to a human interferon-τ polypeptide, serum albumin is derivatized with N-succinimidyl-S-acetyl thioacetate (Duncan), yielding thiolated serum albumin. The activated serum albumin polypeptide is then reacted with human interferon-τ derivatized with N-succinimidyl 3-(2-pyridyldithio) propionate (Cumber), to produce the fused protein joined through a disulfide linkage.

As an alternative method, recombinant human interferon-τ may be prepared with a cysteine residue to allow disulfide coupling of the human interferon-τ to an activated ligand, thus simplifying the coupling reaction. An interferon-τ expression vector, used for production of recombinant human interferon-τ, can be modified for insertion of an internal or a terminal cysteine codon according to standard methods of site-directed mutagenesis (Ausubel, *et al.*).

In one method, a fused protein is prepared recombinantly using an expression vector in which the coding sequence of a second selected polypeptide is joined to the human interferon-τ coding sequence. For example, human serum albumin coding sequences can be fused in-frame to the coding sequence of a human interferon-τ polypeptide, such as, SEQ ID NO:25. The fused protein is then expressed using a suitable host cell. The fusion protein may be purified by molecular-sieve and ion-exchange chromatography methods, with additional purification by polyacrylamide gel electrophoretic separation and/or HPLC chromatography, if necessary.

It will be appreciated from the above how human interferon-τ-containing fusion proteins may be prepared. One variation on the above fusion is to exchange positions of the human interferon-τ and selected second protein molecules in the fusion protein (*e.g.*, carboxy terminal versus amino terminal fusions). Further, internal portions of a native human interferon-τ polypeptide (for example, amino acid regions of between 20 and 172 amino acids) can be assembled into polypeptides where two or more such human interferon-τ portions are contiguous that are normally discontinuous in the native protein.

In addition to the above-described fusion proteins, the present invention also contemplates polypeptide compositions having (a) a human interferon-τ polypeptide, where said polypeptide is (i) derived from the N-terminal portion of a human interferon-τ amino acid coding sequence, and (ii) between 8 and 37 amino acids long, and (b) a second soluble polypeptide. Interferon-α and interferon-β are examples of such second soluble polypeptides. Such hybrid interferon compositions can be encoded by hybrid nucleic acid molecules formed of a 5' end segment that encodes the N-terminal amino acid sequence of an interferon-tau polypeptide, and a 3' end segment that encodes the C-terminal amino acid sequence of a non-tau interferon type I polypeptide. The two segments are spliced in a region corresponding to the portion of a mature interferon polypeptide between about amino acid residues 8 and 37.

The hybrid HuIFNτ polypeptides associated with reduced toxicity may be co-administered with or substituted for more toxic interferons to reduce the toxicity of the more toxic interferons when used in pharmaceutical formulations or in therapeutic applications.

C. Antibodies Reactive with Human Interferon-τ

Fusion proteins containing the polypeptide antigens of the present invention fused with the glutathione-S-transferase (Sj26) protein can be expressed using the pGEX-GLI vector system in *E. coli* JM101 cells. The fused Sj26 protein can be isolated readily by glutathione substrate affinity chromatography (Smith, *et al.*, 1988). Expression and partial purification of HuIFNτ proteins is described in (Example 5), and is applicable to any of the other soluble, induced polypeptides coded by sequences described by the present invention.

Insoluble GST (sj26) fusion proteins can be purified by preparative gel electrophoresis.

Alternatively, HuIFNτ-β-galactosidase fusion proteins can be isolated as described in Example 4.

Also included in the invention is an expression vector, such as the lambda gt11 or pGEX vectors described above, containing HuIFNτ coding sequences and expression control elements which allow expression of the coding regions in a suitable host. The control elements generally include a promoter, translation initiation codon, and translation and transcription termination sequences, and an insertion site for introducing the insert into the vector.

The DNA encoding the desired polypeptide can be cloned into any number of vectors (discussed above) to generate expression of the polypeptide in the appropriate host system. These recombinant polypeptides can be expressed as fusion proteins or as native proteins.

In another aspect, the invention includes specific antibodies directed against the polypeptides of the present invention. Typically, to prepare antibodies, a host animal, such as a rabbit, is immunized with the purified antigen or fused protein antigen. Hybrid, or fused, proteins may be generated using a variety of coding sequences derived from other proteins, such as β-galactosidase or glutathione-S-transferase. The host serum or plasma is collected following an appropriate time interval, and this serum is tested for antibodies specific against the antigen. Example 5 describes the production of rabbit serum antibodies which are specific against the HuIFNτ antigens in a Sj26/HuIFNτ hybrid protein. These techniques can be applied to the all of the HuIFNτ molecules and polypeptides derived therefrom.

The gamma globulin fraction or the IgG antibodies of immunized animals can be obtained, for example, by use of saturated ammonium sulfate or DEAE Sephadex, or other techniques known to those skilled in the art for producing polyclonal antibodies.

Alternatively, purified protein or fused protein may be used for producing monoclonal antibodies. Here the spleen or lymphocytes from a animal immunized with the selected polypeptide antigen are removed and immortalized or used to prepare hybridomas by methods known to those skilled in the art (Harlow, *et al.*). Lymphocytes can be isolated from a

peripheral blood sample. Epstein-Barr virus (EBV) can be used to immortalize human lymphocytes or a fusion partner can be used to produce hybridomas.

Antibodies secreted by the immortalized cells are screened to determine the clones that secrete antibodies of the desired specificity, for example, by using the ELISA or Western blot method (Ausubel, *et al.*).

Antigenic regions of polypeptides are generally relatively small, typically 7 to 10 amino acids in length. Smaller fragments have been identified as antigenic regions. Human interferon-τ polypeptide antigens are identified as described above. The resulting DNA coding regions can be expressed recombinantly either as fusion proteins or isolated polypeptides.

In addition, some amino acid sequences can be conveniently chemically synthesized (Applied Biosystems, Foster City CA). Antigens obtained by any of these methods may be directly used for the generation of antibodies or they may be coupled to appropriate carrier molecules. Many such carriers are known in the art and are commercially available (*e.g.*, Pierce, Rockford IL).

Antibodies reactive with HuIFNτ are useful, for example, in the analysis of structure/function relationships.

V. Utility

A. Reproductive

Although HuIFNτ bears some similarity to the IFNα family based on structure and its potent antiviral properties, the IFNαs do not possess the reproductive properties associated with HuIFNτ. Also, recombinant bovine IFNα has little or no effect on interestrous interval compared to IFNτ (Davis, *et al.*, 1992).

Therefore, although HuIFNτ has some structural similarities to other interferons, it has very distinctive properties of its own: for example, the capability of significantly influencing the biochemical events of the estrous cycle.

The human IFNτ of the present invention can be used in methods of enhancing fertility and prolonging the life span of the *corpus luteum* in female mammals as generally described in Hansen, *et al.*, herein incorporated by reference. Further, the human interferon-τ of the present invention could be used to regulate growth and development of uterine and/or fetal-placental tissues. HuIFNτ is particularly useful for treatment of humans, since potential antigenic responses are less likely using such a same-species protein.

B. Antiviral Properties

The antiviral activity of HuIFNτ has broad therapeutic applications without the toxic effects that are usually associated with IFNαs. HuIFNτ was found to exert its antiviral activity without adverse effects on the cells: no evidence of cytotoxic effects attributable to the administration of HuIFNτ was observed. It is the lack of cytotoxicity of HuIFNτ which makes it extremely valuable as an *in vivo* therapeutic agent. This lack of cytotoxicity sets HuIFNτ apart from most other known antiviral agents and all other known interferons.

HuIFNτ is an effective antiviral agent against a wide variety of viruses, including both RNA and DNA viruses. Human interferon-τ may be used for the treatment of, for example, the following viral diseases: human immunodeficiency virus (HIV), hepatitis c virus (HCV) and hepatitis B virus (HBV). Formulations comprising the HuIFNτ compounds of the present invention can be used to inhibit viral replication.

The human IFNτ of the present invention can be employed in methods for affecting the immune relationship between fetus and mother, for example, in preventing transmission of maternal viruses (*e.g.*, HIV) to the developing fetus. The human interferon-τ is particularly useful for treatment of humans, since potential antigenic responses are less likely using a homologous protein.

C. Anticellular Proliferation Properties

IFNτ exhibits antiproliferative activity against human tumor cells without toxicity and is as potent or more potent than human IFNα. Clinical trials of the IFNα's have shown them to be effective antitumor agents (Dianzani; Krown). One therapeutic advantage of HuIFNτ as a therapeutic is the elimination of toxic effects seen with high doses IFNαs.

One application of the HuIFNτ is against tumors like Kaposi's sarcoma (associated with HIV infection) where the antineoplastic effects of HuIFNτ are coupled with HuIFNτ ability to inhibit retroviral growth.

HuIFNτ exhibits potent anticellular proliferation activity. HuIFNτ can also be used to inhibit cellular growth without the negative side effects associated with other interferons which are currently known. Formulations comprising the HuIFNτ compounds of the subject invention can be used in methods to inhibit, prevent, slow or reduced tumor cell growth, including, but are not limited to, the following types of tumor cells: human carcinoma cells, hematopoietic cancer cells, human leukemia cells, human lymphoma cells, human melanoma cells and steroid-sensitive tumor cells (for example, mammary tumor cells/estrogen-dependent tumor cells).

D. Interfering with the Binding of Interferons to Receptors

IFNτ appears to interact with the Type I IFN receptor via several epitopes on the molecule, and these regions either separately or in combination may differently affect distinct functions of HuIFNτ. The polypeptides of the present invention may be useful for the selective inhibition of binding of interferons to the interferon receptor.

Accordingly, HuIFNτ polypeptides may be used as immunoregulatory molecules when it is desired to prevent immune responses triggered by interferon molecules. Such peptides could be used as immunosuppressants to prevent, for example, interferon-mediated immune responses to tissue transplants. Other types of interferon mediated responses may also be blocked, such as the cytotoxic effects of alpha interferon.

E. Pharmaceutical Compositions

One advantage, for therapeutic applications, of HuIFNτ over other interferons, such as IFNα and IFNβ, is that treatment with therapeutic doses of HuIFNτ does not appear to be associated with cytotoxicity. In particular, HuIFNτ appears to be non-toxic at concentrations at which IFNβ induces toxicity.

HuIFNτ proteins can be formulated according to known methods for preparing pharmaceutically useful compositions. Formulations comprising interferons or interferon-like compounds have been previously described (for example, Martin). In general, the compositions of the subject invention will be formulated such that an effective amount of the HuIFNτ is combined with a suitable carrier in order to facilitate effective administration of the composition.

The compositions used in these therapies may also be in a variety of forms. These include, for example, solid, semi-solid, and liquid dosage forms, such as tablets, pills, powders, liquid solutions or suspensions, liposomes, suppositories, injectable, and infusible solutions. The preferred form depends on the intended mode of administration and therapeutic application. The compositions also preferably include conventional pharmaceutically acceptable carriers and adjuvants which are known to those of skill in the art. Preferably, the compositions of the invention are in the form of a unit dose and will usually be administered to the patient one or more times a day.

HuIFNτ, or related polypeptides, may be administered to a patient (or subject in need of treatment) in any pharmaceutically acceptable dosage form, including intravenous, intramuscular, intralesional, or subcutaneous injection. Specifically, compositions and methods used for other interferon compounds can be used for the delivery of these compounds.

One primary advantage of the compounds of the subject invention, however, is the extremely low cytotoxicity of the HuIFNτ proteins. Because of this low cytotoxicity, it is possible to administer the HuIFNτ in concentrations which are greater than those which can generally be utilized for other interferon (*e.g.*, IFNα) compounds. Thus, HuIFNτ can be administered at rates from about 5×10^4 to 20×10^6 units/day to about 500×10^6 units/day or more. In a preferred embodiment, the dosage is about 20×10^6 units/day. High doses are preferred for systemic administration. It should, of course, be understood that the compositions and methods of this invention may be used in combination with other therapies.

Once improvement of a patient's condition has occurred, a maintenance dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained. When the symptoms have been alleviated to the desired level, treatment should cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

The compositions of the subject invention can be administered through standard procedures to treat a variety of cancers and viral diseases including those for which other interferons have previously shown activity. See, for example, Finter, *et al.*; Dianzani; Francis, *et al.* and U.S. Patent Nos. 4,885,166 and 4,975,276. However, as discussed above, the compositions of the subject invention have unique features and advantages, including their ability to treat these conditions without toxicity.

F. Treatment of Skin Disorders

Disorders of the skin can be treated intralesionally using HuIFNτ, wherein formulation and dose will depend on the method of administration and on the size and severity of the lesion to be treated. Preferred methods include intradermal and subcutaneous injection. Multiple injections into large lesions may be possible, and several lesions on the skin of a single patient may be treated at one time. The schedule for administration can be determined by a person skilled in the art. Formulations designed for sustained release can reduce the frequency of administration.

G. Systemic Treatment

Systemic treatment is essentially equivalent for all applications. Multiple intravenous, subcutaneous and/or intramuscular doses are possible, and in the case of implantable methods

for treatment, formulations designed for sustained release are particularly useful. Patients may also be treated using implantable subcutaneous portals, reservoirs, or pumps.

H. Regional Treatment

Regional treatment with the HuIFNτ polypeptides of the present invention is useful for treatment of cancers in specific organs. Treatment can be accomplished by intraarterial infusion. A catheter can be surgically or angiographically implanted to direct treatment to the affected organ. A subcutaneous portal, connected to the catheter, can be used for chronic treatment, or an implantable, refillable pump may also be employed.

The following examples illustrate, but in no way are intended to limit the present invention.

Materials and Methods

Restriction endonucleases, T4 DNA ligase, T4 polynucleotide kinase, *Taq* DNA polymerase, and calf intestinal phosphatase were purchased from New England Biolabs (Beverly, MA) or Promega Biotech (Madison, WI): these reagents were used according to the manufacturer's instruction. For sequencing reactions, a "SEQUENASE DNA II" sequencing kit was used (United States Biochemical Corporation, Cleveland OH). Immunoblotting and other reagents were from Sigma Chemical Co. (St. Louis, MO) or Fisher Scientific (Needham, MA). Nitrocellulose filters are obtained from Schleicher and Schuell (Keene, NH).

Synthetic oligonucleotide linkers and primers are prepared using commercially available automated oligonucleotide synthesizers (*e.g.*, an ABI model 380B-02 DNA synthesizer (Applied Biosystems, Foster City, CA)). Alternatively, custom designed synthetic oligonucleotides may be purchased, for example, from Synthetic Genetics (San Diego, CA). cDNA synthesis kit and random priming labeling kits are obtained from Boehringer-Mannheim Biochemical (BMB, Indianapolis, IN).

Oligonucleotide sequences encoding polypeptides can be either synthesized directly by standard methods of oligonucleotide synthesis, or, in the case of large coding sequences, synthesized by a series of cloning steps involving a tandem array of multiple oligonucleotide fragments corresponding to the coding sequence (Crea; Yoshio, *et al.*; Eaton *et al.*). Oligonucleotide coding sequences can be expressed by standard recombinant procedures (Maniatis, *et al.*; Ausubel, *et al.*; Rothstein).

Alternatively, peptides can be synthesized directly by standard *in vitro* techniques (Applied Biosystems, Foster City CA).

Common manipulations involved in polyclonal and monoclonal antibody work, including antibody purification from sera, are performed by standard procedures (Harlow, *et al.*). Pierce (Rockford, IL) is a source of many antibody reagents.

Recombinant human IFNα (rHuIFNα) and rBoIFNγ was obtained from Genentech Inc. (South San Francisco, CA). The reference preparation of recombinant human IFNα (rHuIFNα) was obtained from the National Institutes of Health: rHuIFNα is commercially available from Lee Biomolecular (San Diego, CA).

All tissue culture media, sera and IFNs used in this study were negative for endotoxin, as determined by assay with Limulus amebocyte lysate (Associates of Cape Cod, Woods Hole, MA) at a sensitivity level of 0.07 ng/ml.

A. General ELISA Protocol for Detection of Antibodies

Polystyrene 96 well plates Immulon II (PGC) were coated with 5 μg/mL (100 μL per well) antigen in 0.1 M carb/bicarbonate buffer, pH 9.5. Plates were sealed with parafilm and stored at 4°C overnight.

Plates were aspirated and blocked with 300 μL 10% NGS and incubated at 37°C for 1 hr.

Plates were washed 5 times with PBS 0.5% "TWEEN-20".

Antisera were diluted in 0.1 M PBS, pH 7.2. The desired dilution(s) of antisera (0.1 mL) were added to each well and the plate incubated 1 hours at 37°C. The plates was then washed 5 times with PBS 0.5% "TWEEN-20".

Horseradish peroxidase (HRP) conjugated goat anti-human antiserum (Cappel, Durham, NC) was diluted 1/5,000 in PBS. 0.1 mL of this solution was added to each well. The plate was incubated 30 min at 37°C, then washed 5 times with PBS.

Sigma ABTS (substrate) was prepared just prior to addition to the plate.

The reagent consists of 50 mL 0.05 M citric acid, pH 4.2, 0.078 mL 30% hydrogen peroxide solution and 15 mg ABTS. 0.1 mL of the substrate was added to each well, then incubated for 30 min at room temperature. The reaction was stopped with the addition of 0.050 mL 5% SDS (w/v). The relative absorbance is determined at 410 nm.

EXAMPLE 1

Southern Blot Analysis of Human High Molecular Weight DNA

Human venous blood samples from healthy donors were collected in heparinized tubes and peripheral blood lymphocytes were isolated by density-gradient centrifugation using a Ficoll-Isopaque gradient (1.077 g/ml) (Sigma Chemical Co.). High molecular weight (HMW) DNA was isolated from these cells (Sambrook, *et al.*).

Two 10 μg samples of HMW DNA were digested with the restriction endonucleases *Hind*III or *Pst*I (Promega) for 2 hours at 37°C, and the DNA fragments electrophoretically separated in a 0.8% agarose gel (Bio-Rad, Richmond, CA) at 75 volts for 8 hours. The DNA fragments were transferred onto a nylon membrane (IBI-International Biotechnologies, Inc., New Haven, CT). The membrane was baked at 80°C for 2 hours and incubated at 42°C for 4 hours in the following pre-hybridization solution: 5 × SSC (1 × SSC is 0.15 M NaCl and 0.15 M sodium citrate), 50% vol/vol formamide, 0.6% (wt/vol) SDS, 0.5% (wt/vol) nonfat dry milk, 20 mM Tris-HCl (pH 7.5), 4 mM EDTA, and 0.5 mg/ml single stranded herring sperm DNA (Promega).

The filter was then incubated in a hybridization solution (5 × SSC, 20% vol/vol formamide, 0.6% (wt/vol) SDS, 0.5% (wt/vol) nonfat dry milk, 20 mM Tris-HCl (pH 7.5), 4 mM EDTA, and 2 × 10^8 cpm/ml ^{32}P-labelled OvIFNτ cDNA (Imakawa, *et al.*, 1987)) for 18 hours at 42°C. The filter was washed at 42°C for 15 minutes with 2 × SSC and 0.1% (wt/vol) SDS and exposed to X-ray film (XAR, Eastman Kodak, Rochester, NY) at -80°C for 48 hours in the presence of an intensifying screen.

Autoradiography detected a hybridization signal at approximately 3.4 kb in DNA digested with *Pst*I and a slightly smaller (≈ 3.0 kb) fragment in the *Hind*III digested DNA. These results indicate the presence of human DNA sequences complementary to the OvIFNτ cDNA probe.

EXAMPLE 2

Isolation of Partial Sequence of Human IFNτ cDNA by PCR

Two synthetic oligonucleotides (each 25-mer), corresponding to the sequence 231 to 255 (contained in SEQ ID NO:5) and 566 to 590 (contained in SEQ ID NO:6) of OvIFNτ cDNA (numbering relative to the cap site, Imakawa, *et al.*, 1987) were synthesized. These primers contained, respectively, cleavage sites for the restriction endonucleases *Pst*I and *Eco*RI. SEQ ID NO:5 was modified to contain the *EcoRI* site, which begins at position 569.

DNA was isolated from approximately 1×10^5 plaque forming units (pfu) of the following two cDNA libraries: human term placenta (Clontech, Inc., Palo Alto, CA) and human term cytotrophoblast (Dr. J.F. Strauss, University of Pennsylvania, Philadelphia PA). The DNA was employed in polymerase chain reaction (PCR) amplifications (Mullis; Mullis, *et al.*; Perkin Elmer Cetus Corp. Norwalk CT). Amplification reactions were carried out for 30 cycles (45°C, 1m; 72°C, 2m; 94°C, 1m) (thermal cycler and reagents, Perkin Elmer Cetus) using primers SEQ ID NO:5/SEQ ID NO:6.

Amplification products were electrophoretically separated (100 volts in a 1.5% agarose gel (Bio-Rad)) and transferred onto a nylon membrane (IBI). The membrane was baked at 80°C for 2 hours and pre-hybridized and hybridized with ^{32}P-labelled OvIFNτ cDNA as described above. The membrane was washed in 5 × SSC/0.1% (wt/vol) SDS for 5 minutes at 42°C and in 2 × SSC/0.1% (wt/vol) SDS for 2 minutes at 42°C. It was then exposed at -80°C to "XAR" (Eastman Kodak) X-ray film for 24 hours in the presence of an intensifying screen. An amplification product that hybridized with the labelled probe DNA was detected.

PCR was performed again as directed above. Amplified products were digested with the restriction endonucleases *Eco*RI and *Pst*I (Promega) for 90 minutes at 37°C. The resulting DNA fragments were electrophoretically separated as described above and the band containing the HuIFNτ amplification product was excised from the gel. DNA fragments were recovered by electroelution, subcloned into *Eco*RI/*Pst*I digested-dephosphorylated plasmid pUC19 and transformed into *E. coli* strain JM101 (Promega) by calcium chloride method (Sambrook, *et al.*). The plasmids were isolated and the inserted amplification product sequenced using the dideoxy termination method (Sanger, *et al.*; "SEQUENASE" reactions, United States Biochemical, Cleveland, OH). Nucleotide sequences were determined, and comparison of these as well as the deduced amino acid sequences to other IFN sequences were performed using "DNA STAR SOFTWARE" (Madison, WI).

Comparison of the sequences of these clones revealed the following five different clones: from the human placental library, HuIFNτ6 (299 bp; SEQ ID NO:7, SEQ ID NO:8), HuIFNτ7 (288 bp; SEQ ID NO:9, SEQ ID NO:10) and HuIFNτ4 (307 bp; SEQ ID NO:11, SEQ ID NO:12), which exhibit 95% identity in their nucleotide sequences; from the cytotrophoblast library clone CTB 35 (HuIFNτ5; 294 basepairs; SEQ ID NO:13, SEQ ID NO:14), which shares 95% and 98% identity with HuIFNτ6 and HuIFNτ4, respectively.

EXAMPLE 3

Isolation of Full-Length Human IFNτ Genes

Ten micrograms PBMC HMW DNA was digested with restriction endonuclease *Eco*RI and subjected to electrophoretic analysis in a 0.8% agarose gel. A series of samples containing ranges of DNA fragments sized 1.5 to 10 kb (*e.g.*, 1.5 to 2.5 kb, 2.5 kb to 3 kb) were excised from the gel. The DNAs were electroeluted and purified. Each DNA sample was amplified as described above using the OvIFNτ primers. The DNA molecules of any sample that yielded a positive PCR signal were cloned into λgt11 (the subgenomic λgt11 library).

A. PCR Identification of Clones Containing Sequences Complementary to OvIFNτ

The λgt11 phage were then plated for plaques and plaque-lift hybridization performed using the ^{32}P-labelled OvIFNτ cDNA probe. Approximately 20 clones were identified that hybridized to the probe.

Plaques that hybridized to the probe were further analyzed by PCR using the OvIFNτ primers described above. Six plaques which generated positive PCR signals were purified. The phage DNA from these clones was isolated and digested with *Eco*RI restriction endonuclease. The DNA inserts were subcloned into pUC19 vectors and their nucleotide sequences determined by dideoxy nucleotide sequencings.

B. Hybridization Identification of Clones Containing Sequences Complementary to PCR-Positive Phage

Recombinant phage from the λgt11 subgenomic library were propagated in *E. coli* Y1080 and plated with *E. coli* Y1090 at a density of about 20,000 plaques/150 mm plate. The plates were overlaid with duplicate nitrocellulose filters, which were hybridized with a ^{32}P-labelled probe from one of the six human IFNτ cDNA clones isolated above.

Clones giving positive hybridization signals were further screened and purified. The phage DNAs from hybridization-positive clones were isolated, digested with *Eco*RI, subcloned into pUC19 vector and sequenced. The sequence information was then analyzed.

1. HuIFNτ1. Three clones yielded over-lapping sequence information for over 800 bases relative to the mRNA cap site (clones were sequenced in both orientations). The combined nucleic acid sequence information is presented as SEQ ID NO:3 and the predicted protein coding sequence is presented as SEQ ID NO:4. Comparison of the predicted mature protein sequence (SEQ ID NO:30) of this gene to the predicted protein sequence of OvIFNτ is shown in Figure 2.

2. HuIFNτ2, HuIFNτ3. Two additional clones giving positive hybridization signals (HuIFNτ2 and HuIFNτ3) were also screened, purified, and phage DNAs subcloned and sequenced as above. The sequences of these two clones are presented in Figures 3A and 3B. As can be appreciated in Figures 3A and 3B, the nucleotide sequence of both clones (HuIFNτ2 and HuIFNτ3) is homologous to that of HuIFNτ1 and OvIFNτ.

HuIFNτ2 (SEQ ID NO:15), may be a pseudo-gene, as it appears to contain a stop codon at position 115-117. The sequence, SEQ ID NO:15, is presented without the leader sequence. The leader sequence is shown in Figure 4A. As can be seen from the HuIFNτ2 sequence presented in Figure 4A, the first amino acid present in mature HuIFNτ1 (a CYS residue) is not present in the HuIFNτ2 sequence. Accordingly, the predicted amino acid sequence presented as SEQ ID NO:16 corresponds to a mature HuIFNτ protein with the exceptions of the first CYS residue and the internal stop codon.

The internal stop codon in the nucleic acid coding sequence can be modified by standard methods to replace the stop codon with an amino acid codon, for example, encoding GLN. The amino acid GLN is present at this position in the other isolates of human IFNτ (HuIFNτ). Standard recombinant manipulations also allow introduction of the initial CYS residue if so desired.

HuIFNτ3 (SEQ ID NO:17), appears to encode a human IFNτ protein. The translated amino acid sequence of the entire protein, including the leader sequence, is presented as SEQ ID NO:18. The translated amino acid sequence of the mature protein is presented as SEQ ID NO:20 (nucleic acid sequence, SEQ ID NO:19).

EXAMPLE 4

Isolation of Human Interferon-τ Fusion Protein

Sepharose 4B beads conjugated with anti-beta galactosidase is purchased from Promega. The beads are packed in 2 ml column and washed successively with phosphate-buffered saline with 0.02% sodium azide and 10 ml TX buffer (10 mM Tris buffer, pH 7.4, 1% aprotinin).

The HuIFNτ coding sequence (*e.g.*, SEQ ID NO:19, *i.e.*, minus the nucleotides corresponding to the leader sequence) is cloned into the polylinker site of lambda gt11. The HuIFNτ coding sequence is placed in-frame with the amino terminal β-galactosidase coding sequences in lambda gt11. Lysogens infected with gt11/HuIFNτ are used to inoculate 500 ml of NZYDT broth. The culture is incubated at 32°C with aeration to an O.D. of about 0.2 to 0.4, then brought to 43°C quickly in a 43°C water bath for 15 minutes to induce gt11 peptide synthesis, and incubated further at 37°C for 1 hour. The cells are pelleted by centrifugation,

suspended in 10 ml of lysis buffer (10 mM Tris, pH 7.4 containing 2% "TRITON X-100" and 1% aprotinin added just before use.

The resuspended cells are frozen in liquid nitrogen then thawed, resulting in substantially complete cell lysis. The lysate is treated with DNaseI to digest bacterial and phage DNA, as evidenced by a gradual loss of viscosity in the lysate. Non-solubilized material is removed by centrifugation.

The clarified lysate material is loaded on the Sepharose column, the ends of the column closed, and the column placed on a rotary shaker for 2 hrs. at room temperature and 16 hours at 4°C. After the column settles, it is washed with 10 ml of TX buffer. The fused protein is eluted with 0.1 M carbonate/bicarbonate buffer, pH10. Typically, 14 ml of the elution buffer is passed through the column, and the fusion protein is eluted in the first 4-6 ml of eluate.

The eluate containing the fusion protein is concentrated in "CENTRICON-30" cartridges (Amicon, Danvers, Mass.). The final protein concentrate is resuspended in, for example, 400 μl PBS buffer. Protein purity is analyzed by SDS-PAGE.

For polyclonal antibodies, the purified fused protein is injected subcutaneously in Freund's adjuvant in a rabbit. Approximately 1 mg of fused protein is injected at days 0 and 21, and rabbit serum is typically collected at 6 and 8 weeks.

EXAMPLE 5

Preparation of Anti-HuIFNτ Antibody

A. Expression of Glutathione-S-Transferase Fusion Proteins.

The HuIFNτ coding sequence (*e.g.*, SEQ ID NO:19) is cloned into the pGEX vector (Boyer, *et al.*; Frangioni, *et al.*; Guan, *et al.*; Hakes, *et al.*; Smith, *et al.*, 1988). The pGEX vector (Smith, *et al.*, 1988) was modified by insertion of a thrombin cleavage sequence in-frame with the glutathione-S-transferase protein (GST -- sj26 coding sequence). This vector is designated pGEXthr. The HuIFNτ coding sequence is placed in-frame with the sj26-thrombin coding sequences (Guan, *et al.*; Hakes, *et al.*). The HuIFNτ coding sequence insert can be generated by the polymerase chain reaction using PCR primers specific for the insert.

The HuIFNτ fragment is ligated to the linearized pGEXthr vector. The ligation mixture is transformed into *E. coli* and ampicillin resistant colonies are selected. Plasmids are isolated from the ampicillin resistant colonies and analyzed by restriction enzyme digestion to identify clones containing the HuIFNτ insert (vector designated pGEXthr-HuIFNτ).

E. coli strain XL-I Blue is transformed with pGEXthr-HuIFNτ and is grown at 37°C overnight. DNA is prepared from randomly-picked colonies. The presence of the insert

coding sequence is typically confirmed by (i) restriction digest mapping, (ii) hybridization screening using labelled HuIFNτ probes (*i.e.*, Southern analysis), or (iii) direct DNA sequence analysis.

B. Partial Purification of Fusion Proteins

A pGEXthr-HuIFNτ clone is grown overnight. The overnight culture is diluted 1:10 with LB medium containing ampicillin and grown for one hour at 37°C. Alternatively, the overnight culture is diluted 1:100 and grown to OD of 0.5-1.0 before addition of IPTG (isopropylthio-β-galactoside). IPTG (GIBCO-BRL, Gaithersburg MD) is added to a final concentration of 0.2-0.5 mM for the induction of protein expression and the incubation is typically continued for 2-5 hours, preferably 3.5 hours.

Bacterial cells are harvested by centrifugation and resuspended in 1/100 culture volume of MTPBS (150 mM NaCl, 16 mM Na_2HP0_4, 4 mM NaH_2PO_4). Cells are lysed by lysozyme, sonication or French press, and lysates cleared of cellular debris by centrifugation.

An aliquot of the supernatant obtained from IPTG-induced cultures of pGEXthr-HuIFNτ-containing cells and an aliquot of the supernatant obtained from IPTG-induced cultures of pGEXthr-vector alone are analyzed by SDS-polyacrylamide gel electrophoresis followed by Western blotting, as described below.

If necessary, the extracts can be concentrated by ultrafiltration using, for example, a "CENTRICON 10" filter.

Alternatively, the fusion proteins are partially purified over a glutathione agarose affinity column as described in detail by Smith, *et al.*, 1988. In this method, 100 ml cultures are grown overnight. The cultures are diluted to 1 liter, and the cells grown another hour at 37°C. Expression of the fusion proteins is induced using IPTG. The induced cultures are grown at 37°C for 3.5 hours. Cells are harvested and a sonicator used to lyse the cells. Cellular debris is pelleted and the clear lysate loaded onto a glutathione "SEPHAROSE" column. The column is washed with several column volumes. The fusion protein is eluted from the affinity column with reduced glutathione and dialyzed. The HuIFNτ can be liberated from the hybrid protein by treatment with thrombin. The sj26 and HuIFNτ fragments of the hybrid protein can then be separated by size fractionation over columns or on gels.

Alternatively, the HuIFNτ portion of the hybrid protein is released from the column by treatment with thrombin (Guan, *et al.*; Hakes, *et al.*).

C. Antibodies Against the Fusion Protein

The purified Sj26/HuIFNτ fused protein is injected subcutaneously in Freund's adjuvant in a rabbit. Approximately 1 mg of fused protein is injected at days 0 and 21, and rabbit serum is typically collected at 6 and 8 weeks. A second rabbit is similarly immunized with purified Sj26 protein obtained from control bacterial lysate.

Minilysates from the following bacterial cultures are prepared: (1) KM392 cells infected with pGEXthr and pGEXthr containing the HuIFNτ insert; and (2) cells infected with lambda gt11 containing the HuIFNτ insert. The minilysates and a commercial source β-galactosidase are fractionated by SDS-PAGE, and the bands transferred to nitrocellulose filters for Western blotting (Sambrook, *et al.*; Ausubel, *et al.*).

Summarizing the expected results, serum from control (Sj26) rabbits is immunoreactive with each of the Sj26 and Sj26 fused protein antigens. Serum from the animal immunized with Sj26/HuIFNτ fused protein is reactive with all Sj-26 and beta-gal fusion proteins containing HuIFNτ coding sequences, indicating the presence of specific immunoreaction with the HuIFNτ antigen. None of the sera are expected to be immunoreactive with beta-galactosidase.

Anti-HuIFNτ antibody present in the sera from the animal immunized with the Sj26/HuIFNτ is purified by affinity chromatography (using immobilized recombinantly produced HuIFNτ as ligand, essentially as described above in Example 12 for the anti-beta-galactosidase antibody).

While the invention has been described with reference to specific methods and embodiments, it will be appreciated that various modifications and changes may be made without departing from the invention.

SEQUENCE LISTING

(1) GENERAL IFNORMATION:

(i) APPLICANT:
(A) NAME: The Women's Research Institute
(B) ADDRESS: 1010 North Kansas
(C) CITY: Wichita
(D) STATE: KS
(E) COUNTRY: US
(F) POSTAL CODE: 67214

(ii) TITLE OF INVENTION: Human Interferon Tau Compositions and Methods of Use

(iii) NUMBER OF SEQUENCES: 34

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Dehlinger & Associates
(B) STREET: P.O. Box 60850
(C) CITY: Palo Alto
(D) STATE: CA
(E) COUNTRY: USA
(F) ZIP: 94306-0850

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE: 10-MAY-1996

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: US 08/438,753
(B) FILING DATE: 10-MAY-1995

(viii) ATTORNEY/AGENT IFNORMATION:
(A) NAME: Sholtz, Charles K.
(B) REGISTRATION NUMBER: 38,615
(C) REFERENCE/DOCKET NUMBER: 5600-0101.41

(ix) TELECOMMUNICATION IFNORMATION:
(A) TELEPHONE: 415-324-0880
(B) TELEFAX: 415-324-0960

(2) IFNORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 516 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: DNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Ovis aries
(B) STRAIN: Domestic
(D) DEVELOPMENTAL STAGE: Blastula (blastocyst)
(F) TISSUE TYPE: Trophectoderm

(G) CELL TYPE: Mononuclear trophectoderm cells

(vii) IMMEDIATE SOURCE:
(B) CLONE: oTP-1a

(viii) POSITION IN GENOME:
(C) UNITS: bp

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..516

(x) PUBLICATION IFNORMATION:
(A) AUTHORS: Ott, Troy L
Van Heeke, Gino
Johnson, Howard M
Bazer, Fuller W
(B) TITLE: Cloning and Expression in Saccharomyces cerevisiae of a Synthetic Gene for the Type I Trophoblast Interferon Ovine Trophoblast Protein-1:Purification and Antiviral Activity
(C) JOURNAL: J. Interferon Res.
(D) VOLUME: 11
(F) PAGES: 357-364
(G) DATE: 1991
(K) RELEVANT RESIDUES IN SEQ ID NO:1: FROM 1 TO 516

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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TGC TAC CTG TCG CGA AAA CTG ATG CTG GAC GCT CGA GAA AAT TTA AAA      48
Cys Tyr Leu Ser Arg Lys Leu Met Leu Asp Ala Arg Glu Asn Leu Lys
 1               5                  10                  15

CTG CTG GAC CGT ATG AAT CGA TTG TCT CCG CAC AGC TGC CTG CAA GAC      96
Leu Leu Asp Arg Met Asn Arg Leu Ser Pro His Ser Cys Leu Gln Asp
            20                  25                  30

CGG AAA GAC TTC GGT CTG CCG CAG GAA ATG GTT GAA GGT GAC CAA CTG     144
Arg Lys Asp Phe Gly Leu Pro Gln Glu Met Val Glu Gly Asp Gln Leu
        35                  40                  45

CAA AAA GAC CAA GCT TTC CCG GTA CTG TAT GAA ATG CTG CAG CAG TCT     192
Gln Lys Asp Gln Ala Phe Pro Val Leu Tyr Glu Met Leu Gln Gln Ser
    50                  55                  60

TTC AAC CTG TTC TAC ACT GAA CAT TCT TCG GCC GCT TGG GAC ACT ACT     240
Phe Asn Leu Phe Tyr Thr Glu His Ser Ser Ala Ala Trp Asp Thr Thr
65                  70                  75                  80

CTT CTA GAA CAA CTG TGC ACT GGT CTG CAA CAG CAA CTG GAC CAT CTG     288
Leu Leu Glu Gln Leu Cys Thr Gly Leu Gln Gln Gln Leu Asp His Leu
                85                  90                  95

GAC ACT TGC CGT GGC CAG GTT ATG GGT GAA GAA GAC TCT GAA CTG GGT     336
Asp Thr Cys Arg Gly Gln Val Met Gly Glu Glu Asp Ser Glu Leu Gly
            100                 105                 110

AAC ATG GAT CCG ATC GTT ACT GTT AAA AAA TAT TTC CAG GGT ATC TAC     384
Asn Met Asp Pro Ile Val Thr Val Lys Lys Tyr Phe Gln Gly Ile Tyr
        115                 120                 125

GAC TAC CTG CAG GAA AAA GGT TAC TCT GAC TGC GCT TGG GAA ATC GTA     432
Asp Tyr Leu Gln Glu Lys Gly Tyr Ser Asp Cys Ala Trp Glu Ile Val
    130                 135                 140

CGC GTT GAA ATG ATG CGG GCC CTG ACT GTG TCG ACT ACT CTG CAA AAA     480
Arg Val Glu Met Met Arg Ala Leu Thr Val Ser Thr Thr Leu Gln Lys
145                 150                 155                 160
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CGG TTA ACT AAA ATG GGT GGT GAC CTG AAT TCT CCG 516
Arg Leu Thr Lys Met Gly Gly Asp Leu Asn Ser Pro
165 170

(2) IFNORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 172 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: amino acid sequence of a mature OvIFNtau protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Cys Tyr Leu Ser Arg Lys Leu Met Leu Asp Ala Arg Glu Asn Leu Lys
1 5 10 15

Leu Leu Asp Arg Met Asn Arg Leu Ser Pro His Ser Cys Leu Gln Asp
20 25 30

Arg Lys Asp Phe Gly Leu Pro Gln Glu Met Val Glu Gly Asp Gln Leu
35 40 45

Gln Lys Asp Gln Ala Phe Pro Val Leu Tyr Glu Met Leu Gln Gln Ser
50 55 60

Phe Asn Leu Phe Tyr Thr Glu His Ser Ser Ala Ala Trp Asp Thr Thr
65 70 75 80

Leu Leu Glu Gln Leu Cys Thr Gly Leu Gln Gln Gln Leu Asp His Leu
85 90 95

Asp Thr Cys Arg Gly Gln Val Met Gly Glu Glu Asp Ser Glu Leu Gly
100 105 110

Asn Met Asp Pro Ile Val Thr Val Lys Lys Tyr Phe Gln Gly Ile Tyr
115 120 125

Asp Tyr Leu Gln Glu Lys Gly Tyr Ser Asp Cys Ala Trp Glu Ile Val
130 135 140

Arg Val Glu Met Met Arg Ala Leu Thr Val Ser Thr Thr Leu Gln Lys
145 150 155 160

Arg Leu Thr Lys Met Gly Gly Asp Leu Asn Ser Pro
165 170

(2) IFNORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 588 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: HuIFNtau1 Human Interferon Tau coding sequence with a leader sequence.

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..585

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

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ATG GCC TTC GTG CTC TCT CTA CTC ATG GCC CTG GTG CTG GTC AGC TAC      48
Met Ala Phe Val Leu Ser Leu Leu Met Ala Leu Val Leu Val Ser Tyr
 1               5                  10                  15

GGC CCA GGA GGA TCC CTG GGT TGT GAC CTG TCT CAG AAC CAC GTG CTG      96
Gly Pro Gly Gly Ser Leu Gly Cys Asp Leu Ser Gln Asn His Val Leu
            20                  25                  30

GTT GGC AGG AAG AAC CTC AGG CTC CTG GAC GAA ATG AGG AGA CTC TCC     144
Val Gly Arg Lys Asn Leu Arg Leu Leu Asp Glu Met Arg Arg Leu Ser
        35                  40                  45

CCT CGC TTT TGT CTG CAG GAC AGA AAA GAC TTC GCT TTA CCC CAG GAA     192
Pro Arg Phe Cys Leu Gln Asp Arg Lys Asp Phe Ala Leu Pro Gln Glu
    50                  55                  60

ATG GTG GAG GGC GGC CAG CTC CAG GAG GCC CAG GCC ATC TCT GTG CTC     240
Met Val Glu Gly Gly Gln Leu Gln Glu Ala Gln Ala Ile Ser Val Leu
65                  70                  75                  80

CAT GAG ATG CTC CAG CAG AGC TTC AAC CTC TTC CAC ACA GAG CAC TCC     288
His Glu Met Leu Gln Gln Ser Phe Asn Leu Phe His Thr Glu His Ser
                85                  90                  95

TCT GCT GCC TGG GAC ACC ACC CTC CTG GAG CAG CTC CGC ACT GGA CTC     336
Ser Ala Ala Trp Asp Thr Thr Leu Leu Glu Gln Leu Arg Thr Gly Leu
            100                 105                 110

CAT CAG CAG CTG GAC AAC CTG GAT GCC TGC CTG GGG CAG GTG ATG GGA     384
His Gln Gln Leu Asp Asn Leu Asp Ala Cys Leu Gly Gln Val Met Gly
        115                 120                 125

GAG GAA GAC TCT GCC CTG GGA AGG ACG GGC CCC ACC CTG GCT CTG AAG     432
Glu Glu Asp Ser Ala Leu Gly Arg Thr Gly Pro Thr Leu Ala Leu Lys
    130                 135                 140

AGG TAC TTC CAG GGC ATC CAT GTC TAC CTG AAA GAG AAG GGA TAC AGC     480
Arg Tyr Phe Gln Gly Ile His Val Tyr Leu Lys Glu Lys Gly Tyr Ser
145                 150                 155                 160

GAC TGC GCC TGG GAA ACC GTC AGA CTG GAA ATC ATG AGA TCC TTC TCT     528
Asp Cys Ala Trp Glu Thr Val Arg Leu Glu Ile Met Arg Ser Phe Ser
                165                 170                 175

TCA TTA ATC AGC TTG CAA GAA AGG TTA AGA ATG ATG GAT GGA GAC CTG     576
Ser Leu Ile Ser Leu Gln Glu Arg Leu Arg Met Met Asp Gly Asp Leu
            180                 185                 190

AGC TCA CCT TGA                                                    588
Ser Ser Pro
        195
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(2) IFNORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 195 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: predicted amino acid coding sequence of SEQ ID NO:3 (HuIFNtau1).

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

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Met Ala Phe Val Leu Ser Leu Leu Met Ala Leu Val Leu Val Ser Tyr
 1               5                  10                  15

Gly Pro Gly Gly Ser Leu Gly Cys Asp Leu Ser Gln Asn His Val Leu
            20                  25                  30

Val Gly Arg Lys Asn Leu Arg Leu Leu Asp Glu Met Arg Arg Leu Ser
        35                  40                  45

Pro Arg Phe Cys Leu Gln Asp Arg Lys Asp Phe Ala Leu Pro Gln Glu
    50                  55                  60

Met Val Glu Gly Gly Gln Leu Gln Glu Ala Gln Ala Ile Ser Val Leu
65                  70                  75                  80

His Glu Met Leu Gln Gln Ser Phe Asn Leu Phe His Thr Glu His Ser
                85                  90                  95

Ser Ala Ala Trp Asp Thr Thr Leu Leu Glu Gln Leu Arg Thr Gly Leu
            100                 105                 110

His Gln Gln Leu Asp Asn Leu Asp Ala Cys Leu Gly Gln Val Met Gly
        115                 120                 125

Glu Glu Asp Ser Ala Leu Gly Arg Thr Gly Pro Thr Leu Ala Leu Lys
    130                 135                 140

Arg Tyr Phe Gln Gly Ile His Val Tyr Leu Lys Glu Lys Gly Tyr Ser
145                 150                 155                 160

Asp Cys Ala Trp Glu Thr Val Arg Leu Glu Ile Met Arg Ser Phe Ser
                165                 170                 175

Ser Leu Ile Ser Leu Gln Glu Arg Leu Arg Met Met Asp Gly Asp Leu
            180                 185                 190

Ser Ser Pro
        195
```

(2) IFNORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (synthetic)

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: 25-mer synthetic oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CCTGTCTGCA GGACAGAAAA GACTT 25

(2) IFNORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (synthetic)

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: 25-mer synthetic oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

TCTGAATTCT GACGATTTCC CAGGC 25

(2) IFNORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 299 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA to mRNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: HuIFNtau6

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..298

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

```
C CAG GAG ATG GTG GAG GGC GGC CAG CTC CAG GAG GCC CAG GCC ATC          46
  Gln Glu Met Val Glu Gly Gly Gln Leu Gln Glu Ala Gln Ala Ile
    1               5                  10                  15

TCT GTG CTC CAC AAG ATG CTC CAG CAG AGC TTC AAC CTC TTC CAC ACA        94
Ser Val Leu His Lys Met Leu Gln Gln Ser Phe Asn Leu Phe His Thr
                20                  25                  30

GAG CGC TCC TCT GCT GCC TGG GAC ACC ACC CTC CTG GAG CAG CTC CGC       142
Glu Arg Ser Ser Ala Ala Trp Asp Thr Thr Leu Leu Glu Gln Leu Arg
            35                  40                  45

ACT GGA CTC CAT CAG CAG CTG GAT GAC CTG GAC GCC TGC CTG GGG CAG       190
Thr Gly Leu His Gln Gln Leu Asp Asp Leu Asp Ala Cys Leu Gly Gln
        50                  55                  60
```

GTG ACG GGA GAG GAA GAC TCT GCC CTG GGA AGG ACG GGC CCC ACC CTG 238
Val Thr Gly Glu Glu Asp Ser Ala Leu Gly Arg Thr Gly Pro Thr Leu
65 70 75

GCC GTG AAG AGC TAC TTC CAG GGC ATC CAT ATC TAC CTG CAA GAG AAG 286
Ala Val Lys Ser Tyr Phe Gln Gly Ile His Ile Tyr Leu Gln Glu Lys
80 85 90 95

GGA TAC AGC GAC T 299
Gly Tyr Ser Asp

(2) IFNORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 99 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: predicted amino acid coding sequence of SEQ ID NO:7 (HuIFNtau6).

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Gln Glu Met Val Glu Gly Gly Gln Leu Gln Glu Ala Gln Ala Ile Ser
1 5 10 15

Val Leu His Lys Met Leu Gln Gln Ser Phe Asn Leu Phe His Thr Glu
20 25 30

Arg Ser Ser Ala Ala Trp Asp Thr Thr Leu Leu Glu Gln Leu Arg Thr
35 40 45

Gly Leu His Gln Gln Leu Asp Asp Leu Asp Ala Cys Leu Gly Gln Val
50 55 60

Thr Gly Glu Glu Asp Ser Ala Leu Gly Arg Thr Gly Pro Thr Leu Ala
65 70 75 80

Val Lys Ser Tyr Phe Gln Gly Ile His Ile Tyr Leu Gln Glu Lys Gly
85 90 95

Tyr Ser Asp

(2) IFNORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 288 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA to mRNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: HuIFNtau7

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..286

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

```
C CAG GAG ATG GTG GAG GTC AGC CAG TTC CAG GAG GCC CAG GCC ATT          46
  Gln Glu Met Val Glu Val Ser Gln Phe Gln Glu Ala Gln Ala Ile
    1               5                  10                  15

TCT GTG CTC CAT GAG ATG CTC CAG CAG AGC TTC AAC CTC TTC CAC AAA        94
Ser Val Leu His Glu Met Leu Gln Gln Ser Phe Asn Leu Phe His Lys
                  20                  25                  30

GAG CGC TCC TCT GCT GCC TGG GAC ACT ACC CTC CTG GAG CAG CTC CTC       142
Glu Arg Ser Ser Ala Ala Trp Asp Thr Thr Leu Leu Glu Gln Leu Leu
              35                  40                  45

ACT GGA CTC CAT CAG CAG CTG GAT GAC CTG GAT GCC TGT CTG GGG CAG       190
Thr Gly Leu His Gln Gln Leu Asp Asp Leu Asp Ala Cys Leu Gly Gln
          50                  55                  60

TTG ACT GGA GAG GAA GAC TCT GCC CTG GGA AGG ACG GGC CCC ACC CTG       238
Leu Thr Gly Glu Glu Asp Ser Ala Leu Gly Arg Thr Gly Pro Thr Leu
      65                  70                  75

GCC GTG AAG AGC TAC TTC CAG GGC ATC CAT GTC TAC CTG CAA GAG AAG       286
Ala Val Lys Ser Tyr Phe Gln Gly Ile His Val Tyr Leu Gln Glu Lys
  80                  85                  90                  95

GG                                                                    288
```

(2) IFNORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 95 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: predicted amino acid coding sequence of SEQ ID NO:9 (HuIFNtau7).

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```
Gln Glu Met Val Glu Val Ser Gln Phe Gln Glu Ala Gln Ala Ile Ser
 1               5                  10                  15

Val Leu His Glu Met Leu Gln Gln Ser Phe Asn Leu Phe His Lys Glu
            20                  25                  30

Arg Ser Ser Ala Ala Trp Asp Thr Thr Leu Leu Glu Gln Leu Leu Thr
        35                  40                  45

Gly Leu His Gln Gln Leu Asp Asp Leu Asp Ala Cys Leu Gly Gln Leu
    50                  55                  60

Thr Gly Glu Glu Asp Ser Ala Leu Gly Arg Thr Gly Pro Thr Leu Ala
65                  70                  75                  80

Val Lys Ser Tyr Phe Gln Gly Ile His Val Tyr Leu Gln Glu Lys
                85                  90                  95
```

(2) IFNORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 307 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA to mRNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: HuIFNtau4

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..307

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

```
C CAG GAG ATG GTG GAG GGT GGC CAG CTC CAG GAG GCC CAG GCC ATC          46
  Gln Glu Met Val Glu Gly Gly Gln Leu Gln Glu Ala Gln Ala Ile
    1               5                  10                  15

TCT GTG CTC CAC GAG ATG CTC CAG CAG AGC TTC AAC CTC TTC CAC ACA        94
Ser Val Leu His Glu Met Leu Gln Gln Ser Phe Asn Leu Phe His Thr
                20                  25                  30

GAG CAC TCC TCT GCT GCC TGG GAC ACC ACC CTC CTG GAG CAG CTC CGC       142
Glu His Ser Ser Ala Ala Trp Asp Thr Thr Leu Leu Glu Gln Leu Arg
            35                  40                  45

ACT GGA CTC CAT CAG CAG CTG GAT GAC CTG GAT GCC TGC CTG GGG CAG       190
Thr Gly Leu His Gln Gln Leu Asp Asp Leu Asp Ala Cys Leu Gly Gln
        50                  55                  60

GTG ACG GGA GAG GAA GAC TCT GCC CTG GGA AGG ACG GGC CCC ACC CTG       238
Val Thr Gly Glu Glu Asp Ser Ala Leu Gly Arg Thr Gly Pro Thr Leu
    65                  70                  75

GCC ATG AAG ACG TAT TTC CAG GGC ATC CAT GTC TAC CTG AAA GAG AAG       286
Ala Met Lys Thr Tyr Phe Gln Gly Ile His Val Tyr Leu Lys Glu Lys
80                  85                  90                  95

GGA TAT AGT GAC TGC GCC TGG                                           307
Gly Tyr Ser Asp Cys Ala Trp
                100
```

(2) IFNORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 102 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: predicted amino acid coding sequence of SEQ ID NO:11 (HuIFNtau4).

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Gln Glu Met Val Glu Gly Gly Gln Leu Gln Glu Ala Gln Ala Ile Ser
1 5 10 15

Val Leu His Glu Met Leu Gln Gln Ser Phe Asn Leu Phe His Thr Glu
20 25 30

His Ser Ser Ala Ala Trp Asp Thr Thr Leu Leu Glu Gln Leu Arg Thr
35 40 45

Gly Leu His Gln Gln Leu Asp Asp Leu Asp Ala Cys Leu Gly Gln Val
50 55 60

Thr Gly Glu Glu Asp Ser Ala Leu Gly Arg Thr Gly Pro Thr Leu Ala
65 70 75 80

Met Lys Thr Tyr Phe Gln Gly Ile His Val Tyr Leu Lys Glu Lys Gly
85 90 95

Tyr Ser Asp Cys Ala Trp
100

(2) IFNORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 294 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA to mRNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: HuIFNtau5

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..292

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

C CAG GAG ATG GTG GAG GGT GGC CAG CTC CAG GAG GCC CAG GCC ATC 46
Gln Glu Met Val Glu Gly Gly Gln Leu Gln Glu Ala Gln Ala Ile
1 5 10 15

TCT GTG CTC CAC GAG ATG CTC CAG CAG AGC TTC AAC CTC TTC CAC ACA 94
Ser Val Leu His Glu Met Leu Gln Gln Ser Phe Asn Leu Phe His Thr
20 25 30

GAG CAC TCC TCT GCT GCC TGG GAC ACC ACC CTC CTG GAG CAG CTC CGC 142
Glu His Ser Ser Ala Ala Trp Asp Thr Thr Leu Leu Glu Gln Leu Arg
35 40 45

ACT GGA CTC CAT CAG CAG CTG GAT GAC CTG GAT GCC TGC CTG GGG CAG 190
Thr Gly Leu His Gln Gln Leu Asp Asp Leu Asp Ala Cys Leu Gly Gln
50 55 60

GTG ACG GGA GAG GAA GAC TCT GCC CTG GGA AGG ACG GGC CCC ACC CTG 238
Val Thr Gly Glu Glu Asp Ser Ala Leu Gly Arg Thr Gly Pro Thr Leu
65 70 75

GCC ATG AAG ACG TAT TTC CAG GGC ATC CAT GTC TAC CTG AAA GAG AAG 286
Ala Met Lys Thr Tyr Phe Gln Gly Ile His Val Tyr Leu Lys Glu Lys
80 85 90 95

GGA TAT AG 294
Gly Tyr

(2) IFNORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 97 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: predicted amino acid coding sequence of SEQ ID NO:13 (HuIFNtau5).

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Gln Glu Met Val Glu Gly Gly Gln Leu Gln Glu Ala Gln Ala Ile Ser
1 5 10 15

Val Leu His Glu Met Leu Gln Gln Ser Phe Asn Leu Phe His Thr Glu
20 25 30

His Ser Ser Ala Ala Trp Asp Thr Thr Leu Leu Glu Gln Leu Arg Thr
35 40 45

Gly Leu His Gln Gln Leu Asp Asp Leu Asp Ala Cys Leu Gly Gln Val
50 55 60

Thr Gly Glu Glu Asp Ser Ala Leu Gly Arg Thr Gly Pro Thr Leu Ala
65 70 75 80

Met Lys Thr Tyr Phe Gln Gly Ile His Val Tyr Leu Lys Glu Lys Gly
85 90 95

Tyr

(2) IFNORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 515 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: HuIFNtau2

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..513

(ix) FEATURE:
(A) NAME/KEY: Modified-site

(B) LOCATION: 115-117
(D) OTHER IFNORMATION: /note= "to allow expression of the encoded protein this site can be modified to encode an amino acid, e.g., Gln"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

```
GAC CTG TCT CAG AAC CAC GTG CTG GTT GGC AGG AAG AAC CTC AGG CTC      48
Asp Leu Ser Gln Asn His Val Leu Val Gly Arg Lys Asn Leu Arg Leu
 1               5                  10                  15

CTG GAC CAA ATG AGG AGA CTC TCC CCT CGC TTT TGT CTG CAG GAC AGA      96
Leu Asp Gln Met Arg Arg Leu Ser Pro Arg Phe Cys Leu Gln Asp Arg
            20                  25                  30

AAA GAC TTC GCT TTA CCC TAG GAA ATG GTG GAG GGC GGC CAG CTC CAG     144
Lys Asp Phe Ala Leu Pro     Glu Met Val Glu Gly Gly Gln Leu Gln
        35                  40                  45

GAG GCC CAG GCC ATC TCT GTG CTC CAT GAG ATG CTC CAG CAG AGC TTC     192
Glu Ala Gln Ala Ile Ser Val Leu His Glu Met Leu Gln Gln Ser Phe
    50                  55                  60

AAC CTC TTC CAC ACA GAG CAC TCC TCT GCT GCC TGG GAC ACC ACC CTC     240
Asn Leu Phe His Thr Glu His Ser Ser Ala Ala Trp Asp Thr Thr Leu
65                  70                  75                  80

CTG GAG CAG CTC CGC ACT GGA CTC CAT CAG CAG CTG GAC AAC CTG GAT     288
Leu Glu Gln Leu Arg Thr Gly Leu His Gln Gln Leu Asp Asn Leu Asp
                85                  90                  95

GCC TGC CTG GGG CAG GTG ATG GGA GAG GAA GAC TCT GCC CTG GGA AGG     336
Ala Cys Leu Gly Gln Val Met Gly Glu Glu Asp Ser Ala Leu Gly Arg
            100                 105                 110

ACG GGC CCC ACC CTG GCT CTG AAG AGG TAC TTC CAG GGC ATC CAT GTC     384
Thr Gly Pro Thr Leu Ala Leu Lys Arg Tyr Phe Gln Gly Ile His Val
        115                 120                 125

TAC CTG AAA GAG AAG GGA TAC AGC GAC TGC GCC TGG GAA ACC GTC AGA     432
Tyr Leu Lys Glu Lys Gly Tyr Ser Asp Cys Ala Trp Glu Thr Val Arg
    130                 135                 140

GTG GAA ATC ATG AGA TCC TTC TCT TCA TTA ATC AGC TTG CAA GAA AGG     480
Val Glu Ile Met Arg Ser Phe Ser Ser Leu Ile Ser Leu Gln Glu Arg
145                 150                 155                 160

TTA AGA ATG ATG GAT GGA GAC CTG AGC TCA CCT TG                      515
Leu Arg Met Met Asp Gly Asp Leu Ser Ser Pro
                165                 170
```

(2) IFNORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 171 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: predicted amino acid coding sequence of SEQ ID NO:15 (HuIFNtau2).

(ix) FEATURE:
(A) NAME/KEY: Modified-site

(B) LOCATION: 39
(D) OTHER IFNORMATION: /note= "where Xaa a selected amino acid, for example, Gln"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

```
Asp Leu Ser Gln Asn His Val Leu Val Gly Arg Lys Asn Leu Arg Leu
 1               5                  10                  15

Leu Asp Gln Met Arg Arg Leu Ser Pro Arg Phe Cys Leu Gln Asp Arg
            20                  25                  30

Lys Asp Phe Ala Leu Pro Xaa Glu Met Val Glu Gly Gly Gln Leu Gln
        35                  40                  45

Glu Ala Gln Ala Ile Ser Val Leu His Glu Met Leu Gln Gln Ser Phe
    50                  55                  60

Asn Leu Phe His Thr Glu His Ser Ser Ala Ala Trp Asp Thr Thr Leu
65                  70                  75                  80

Leu Glu Gln Leu Arg Thr Gly Leu His Gln Gln Leu Asp Asn Leu Asp
                85                  90                  95

Ala Cys Leu Gly Gln Val Met Gly Glu Glu Asp Ser Ala Leu Gly Arg
            100                 105                 110

Thr Gly Pro Thr Leu Ala Leu Lys Arg Tyr Phe Gln Gly Ile His Val
        115                 120                 125

Tyr Leu Lys Glu Lys Gly Tyr Ser Asp Cys Ala Trp Glu Thr Val Arg
    130                 135                 140

Val Glu Ile Met Arg Ser Phe Ser Ser Leu Ile Ser Leu Gln Glu Arg
145                 150                 155                 160

Leu Arg Met Met Asp Gly Asp Leu Ser Ser Pro
                165                 170
```

(2) IFNORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 587 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: HuIFNtau3, with leader seq.

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..585

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

```
ATG GCC TTC GTG CTC TCT CTA CTC ATG GCC CTG GTG CTG GTC AGC TAC      48
Met Ala Phe Val Leu Ser Leu Leu Met Ala Leu Val Leu Val Ser Tyr
 1               5                  10                  15

GGC CCG GGA GGA TCC CTG CGG TGT GAC CTG TCT CAG AAC CAC GTG CTG      96
Gly Pro Gly Gly Ser Leu Arg Cys Asp Leu Ser Gln Asn His Val Leu
            20                  25                  30

GTT GGC AGC CAG AAC CTC AGG CTC CTG GGC CAA ATG AGG AGA CTC TCC     144
Val Gly Ser Gln Asn Leu Arg Leu Leu Gly Gln Met Arg Arg Leu Ser
        35                  40                  45

CTT CGC TTC TGT CTG CAG GAC AGA AAA GAC TTC GCT TTC CCC CAG GAG     192
Leu Arg Phe Cys Leu Gln Asp Arg Lys Asp Phe Ala Phe Pro Gln Glu
    50                  55                  60

ATG GTG GAG GGT GGC CAG CTC CAG GAG GCC CAG GCC ATC TCT GTG CTC     240
Met Val Glu Gly Gly Gln Leu Gln Glu Ala Gln Ala Ile Ser Val Leu
65                  70                  75                  80

CAC GAG ATG CTC CAG CAG AGC TTC AAC CTC TTC CAC ACA GAG CAC TCC     288
His Glu Met Leu Gln Gln Ser Phe Asn Leu Phe His Thr Glu His Ser
                85                  90                  95

TCT GCT GCC TGG GAC ACC ACC CTC CTG GAG CAG CTC CGC ACT GGA CTC     336
Ser Ala Ala Trp Asp Thr Thr Leu Leu Glu Gln Leu Arg Thr Gly Leu
            100                 105                 110

CAT CAG CAG CTG GAT GAC CTG GAT GCC TGC CTG GGG CAG GTG ACG GGA     384
His Gln Gln Leu Asp Asp Leu Asp Ala Cys Leu Gly Gln Val Thr Gly
        115                 120                 125

GAG GAA GAC TCT GCC CTG GGA AGA ACG GGC CCC ACC CTG GCC ATG AAG     432
Glu Glu Asp Ser Ala Leu Gly Arg Thr Gly Pro Thr Leu Ala Met Lys
    130                 135                 140

AGG TAT TTC CAG GGC ATC CAT GTC TAC CTG AAA GAG AAG GGA TAT AGT     480
Arg Tyr Phe Gln Gly Ile His Val Tyr Leu Lys Glu Lys Gly Tyr Ser
145                 150                 155                 160

GAC TGC GCC TGG GAA ATT GTC AGA CTG GAA ATC ATG AGA TCC TTG TCT     528
Asp Cys Ala Trp Glu Ile Val Arg Leu Glu Ile Met Arg Ser Leu Ser
                165                 170                 175

TCA TCA ACC AGC TTG CAC AAA AGG TTA AGA ATG ATG GAT GGA GAC CTG     576
Ser Ser Thr Ser Leu His Lys Arg Leu Arg Met Met Asp Gly Asp Leu
            180                 185                 190

AGC TCA CCT TG                                                     587
Ser Ser Pro
        195
```

(2) IFNORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 195 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: predicted amino acid coding sequence of SEQ ID NO:17 (HuIFNtau3)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

```
Met Ala Phe Val Leu Ser Leu Leu Met Ala Leu Val Leu Val Ser Tyr
 1               5                  10                  15

Gly Pro Gly Gly Ser Leu Arg Cys Asp Leu Ser Gln Asn His Val Leu
            20                  25                  30

Val Gly Ser Gln Asn Leu Arg Leu Leu Gly Gln Met Arg Arg Leu Ser
        35                  40                  45

Leu Arg Phe Cys Leu Gln Asp Arg Lys Asp Phe Ala Phe Pro Gln Glu
    50                  55                  60

Met Val Glu Gly Gly Gln Leu Gln Glu Ala Gln Ala Ile Ser Val Leu
65                  70                  75                  80

His Glu Met Leu Gln Gln Ser Phe Asn Leu Phe His Thr Glu His Ser
                85                  90                  95

Ser Ala Ala Trp Asp Thr Thr Leu Leu Glu Gln Leu Arg Thr Gly Leu
            100                 105                 110

His Gln Gln Leu Asp Asp Leu Asp Ala Cys Leu Gly Gln Val Thr Gly
        115                 120                 125

Glu Glu Asp Ser Ala Leu Gly Arg Thr Gly Pro Thr Leu Ala Met Lys
    130                 135                 140

Arg Tyr Phe Gln Gly Ile His Val Tyr Leu Lys Glu Lys Gly Tyr Ser
145                 150                 155                 160

Asp Cys Ala Trp Glu Ile Val Arg Leu Glu Ile Met Arg Ser Leu Ser
                165                 170                 175

Ser Ser Thr Ser Leu His Lys Arg Leu Arg Met Met Asp Gly Asp Leu
            180                 185                 190

Ser Ser Pro
        195
```

(2) IFNORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 518 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: HuIFNtau3, mature, no leader sequence

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..516

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

```
TGT GAC CTG TCT CAG AAC CAC GTG CTG GTT GGC AGC CAG AAC CTC AGG          48
Cys Asp Leu Ser Gln Asn His Val Leu Val Gly Ser Gln Asn Leu Arg
 1               5                  10                  15

CTC CTG GGC CAA ATG AGG AGA CTC TCC CTT CGC TTC TGT CTG CAG GAC          96
Leu Leu Gly Gln Met Arg Arg Leu Ser Leu Arg Phe Cys Leu Gln Asp
            20                  25                  30

AGA AAA GAC TTC GCT TTC CCC CAG GAG ATG GTG GAG GGT GGC CAG CTC         144
Arg Lys Asp Phe Ala Phe Pro Gln Glu Met Val Glu Gly Gly Gln Leu
        35                  40                  45

CAG GAG GCC CAG GCC ATC TCT GTG CTC CAC GAG ATG CTC CAG CAG AGC         192
Gln Glu Ala Gln Ala Ile Ser Val Leu His Glu Met Leu Gln Gln Ser
    50                  55                  60

TTC AAC CTC TTC CAC ACA GAG CAC TCC TCT GCT GCC TGG GAC ACC ACC         240
Phe Asn Leu Phe His Thr Glu His Ser Ser Ala Ala Trp Asp Thr Thr
65                  70                  75                  80

CTC CTG GAG CAG CTC CGC ACT GGA CTC CAT CAG CAG CTG GAT GAC CTG         288
Leu Leu Glu Gln Leu Arg Thr Gly Leu His Gln Gln Leu Asp Asp Leu
                85                  90                  95

GAT GCC TGC CTG GGG CAG GTG ACG GGA GAG GAA GAC TCT GCC CTG GGA         336
Asp Ala Cys Leu Gly Gln Val Thr Gly Glu Glu Asp Ser Ala Leu Gly
            100                 105                 110

AGA ACG GGC CCC ACC CTG GCC ATG AAG AGG TAT TTC CAG GGC ATC CAT         384
Arg Thr Gly Pro Thr Leu Ala Met Lys Arg Tyr Phe Gln Gly Ile His
        115                 120                 125

GTC TAC CTG AAA GAG AAG GGA TAT AGT GAC TGC GCC TGG GAA ATT GTC         432
Val Tyr Leu Lys Glu Lys Gly Tyr Ser Asp Cys Ala Trp Glu Ile Val
    130                 135                 140

AGA CTG GAA ATC ATG AGA TCC TTG TCT TCA TCA ACC AGC TTG CAC AAA         480
Arg Leu Glu Ile Met Arg Ser Leu Ser Ser Ser Thr Ser Leu His Lys
145                 150                 155                 160

AGG TTA AGA ATG ATG GAT GGA GAC CTG AGC TCA CCT TG                      518
Arg Leu Arg Met Met Asp Gly Asp Leu Ser Ser Pro
                165                 170
```

(2) IFNORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 172 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

```
Cys Asp Leu Ser Gln Asn His Val Leu Val Gly Ser Gln Asn Leu Arg
 1               5                  10                  15

Leu Leu Gly Gln Met Arg Arg Leu Ser Leu Arg Phe Cys Leu Gln Asp
            20                  25                  30

Arg Lys Asp Phe Ala Phe Pro Gln Glu Met Val Glu Gly Gly Gln Leu
        35                  40                  45
```

Gln Glu Ala Gln Ala Ile Ser Val Leu His Glu Met Leu Gln Gln Ser
50 55 60

Phe Asn Leu Phe His Thr Glu His Ser Ser Ala Ala Trp Asp Thr Thr
65 70 75 80

Leu Leu Glu Gln Leu Arg Thr Gly Leu His Gln Gln Leu Asp Asp Leu
85 90 95

Asp Ala Cys Leu Gly Gln Val Thr Gly Glu Glu Asp Ser Ala Leu Gly
100 105 110

Arg Thr Gly Pro Thr Leu Ala Met Lys Arg Tyr Phe Gln Gly Ile His
115 120 125

Val Tyr Leu Lys Glu Lys Gly Tyr Ser Asp Cys Ala Trp Glu Ile Val
130 135 140

Arg Leu Glu Ile Met Arg Ser Leu Ser Ser Ser Thr Ser Leu His Lys
145 150 155 160

Arg Leu Arg Met Met Asp Gly Asp Leu Ser Ser Pro
165 170

(2) IFNORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Amino acid sequence of fragment 1-37 of SEQ ID NO:20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

Cys Asp Leu Ser Gln Asn His Val Leu Val Gly Ser Gln Asn Leu Arg
1 5 10 15

Leu Leu Gly Gln Met Arg Arg Leu Ser Leu Arg Phe Cys Leu Gln Asp
20 25 30

Arg Lys Asp Phe Ala
35

(2) IFNORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Amino acid sequence of fragment 34-64 of SEQ ID NO:20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Lys Asp Phe Ala Phe Pro Gln Glu Met Val Glu Gly Gly Gln Leu Gln
1 5 10 15

Glu Ala Gln Ala Ile Ser Val Leu His Glu Met Leu Gln Gln Ser
20 25 30

(2) IFNORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Amino acid sequence of fragment 62-92 of SEQ ID NO:20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Gln Gln Ser Phe Asn Leu Phe His Thr Glu His Ser Ser Ala Ala Trp
1 5 10 15

Asp Thr Thr Leu Leu Glu Gln Leu Arg Thr Gly Leu His Gln Gln
20 25 30

(2) IFNORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Amino acid sequence of fragment 90-122 of SEQ ID NO:20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

His Gln Gln Leu Asp Asp Leu Asp Ala Cys Leu Gly Gln Val Thr Gly
1 5 10 15

Glu Glu Asp Ser Ala Leu Gly Arg Thr Gly Pro Thr Leu Ala Met Lys
20 25 30

Arg

(2) IFNORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: Amino acid sequence of fragment 119-150 of SEQ ID NO:20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Ala Met Lys Arg Tyr Phe Gln Gly Ile His Val Tyr Leu Lys Glu Lys
1 5 10 15

Gly Tyr Ser Asp Cys Ala Trp Glu Ile Val Arg Leu Glu Ile Met Arg
20 25 30

(2) IFNORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Amino acid sequence of fragment 139-172 of SEQ ID NO:20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Cys Ala Trp Glu Ile Val Arg Leu Glu Ile Met Arg Ser Leu Ser Ser
1 5 10 15

Ser Thr Ser Leu His Lys Arg Leu Arg Met Met Asp Gly Asp Leu Ser
20 25 30

Ser Pro

(2) IFNORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Amino acid sequence of fragment 1-23 of SEQ ID NO:18

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Met Ala Phe Val Leu Ser Leu Leu Met Ala Leu Val Leu Val Ser Tyr
1 5 10 15

Gly Pro Gly Gly Ser Leu Arg
20

(2) IFNORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Amino acid sequence of fragment 1-23 of SEQ ID NO:4

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```
Met Ala Phe Val Leu Ser Leu Leu Met Ala Leu Val Leu Val Ser Tyr
 1               5                  10                  15

Gly Pro Gly Gly Ser Leu Gly
            20
```

(2) IFNORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 519 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: HuIFNtau1 genomic-derived DNA coding sequence, without leader seq.

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..516

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

```
TGT GAC CTG TCT CAG AAC CAC GTG CTG GTT GGC AGG AAG AAC CTC AGG      48
Cys Asp Leu Ser Gln Asn His Val Leu Val Gly Arg Lys Asn Leu Arg
 1               5                  10                  15

CTC CTG GAC GAA ATG AGG AGA CTC TCC CCT CGC TTT TGT CTG CAG GAC      96
Leu Leu Asp Glu Met Arg Arg Leu Ser Pro Arg Phe Cys Leu Gln Asp
            20                  25                  30

AGA AAA GAC TTC GCT TTA CCC CAG GAA ATG GTG GAG GGC GGC CAG CTC     144
Arg Lys Asp Phe Ala Leu Pro Gln Glu Met Val Glu Gly Gly Gln Leu
        35                  40                  45

CAG GAG GCC CAG GCC ATC TCT GTG CTC CAT GAG ATG CTC CAG CAG AGC     192
Gln Glu Ala Gln Ala Ile Ser Val Leu His Glu Met Leu Gln Gln Ser
    50                  55                  60

TTC AAC CTC TTC CAC ACA GAG CAC TCC TCT GCT GCC TGG GAC ACC ACC     240
Phe Asn Leu Phe His Thr Glu His Ser Ser Ala Ala Trp Asp Thr Thr
65                  70                  75                  80

CTC CTG GAG CAG CTC CGC ACT GGA CTC CAT CAG CAG CTG GAC AAC CTG     288
Leu Leu Glu Gln Leu Arg Thr Gly Leu His Gln Gln Leu Asp Asn Leu
                85                  90                  95

GAT GCC TGC CTG GGG CAG GTG ATG GGA GAG GAA GAC TCT GCC CTG GGA     336
Asp Ala Cys Leu Gly Gln Val Met Gly Glu Glu Asp Ser Ala Leu Gly
            100                 105                 110
```

AGG ACG GGC CCC ACC CTG GCT CTG AAG AGG TAC TTC CAG GGC ATC CAT 384
Arg Thr Gly Pro Thr Leu Ala Leu Lys Arg Tyr Phe Gln Gly Ile His
115 120 125

GTC TAC CTG AAA GAG AAG GGA TAC AGC GAC TGC GCC TGG GAA ACC GTC 432
Val Tyr Leu Lys Glu Lys Gly Tyr Ser Asp Cys Ala Trp Glu Thr Val
130 135 140

AGA CTG GAA ATC ATG AGA TCC TTC TCT TCA TTA ATC AGC TTG CAA GAA 480
Arg Leu Glu Ile Met Arg Ser Phe Ser Ser Leu Ile Ser Leu Gln Glu
145 150 155 160

AGG TTA AGA ATG ATG GAT GGA GAC CTG AGC TCA CCT TGA 519
Arg Leu Arg Met Met Asp Gly Asp Leu Ser Ser Pro
165 170

(2) IFNORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 172 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Cys Asp Leu Ser Gln Asn His Val Leu Val Gly Arg Lys Asn Leu Arg
1 5 10 15

Leu Leu Asp Glu Met Arg Arg Leu Ser Pro Arg Phe Cys Leu Gln Asp
20 25 30

Arg Lys Asp Phe Ala Leu Pro Gln Glu Met Val Glu Gly Gly Gln Leu
35 40 45

Gln Glu Ala Gln Ala Ile Ser Val Leu His Glu Met Leu Gln Gln Ser
50 55 60

Phe Asn Leu Phe His Thr Glu His Ser Ser Ala Ala Trp Asp Thr Thr
65 70 75 80

Leu Leu Glu Gln Leu Arg Thr Gly Leu His Gln Gln Leu Asp Asn Leu
85 90 95

Asp Ala Cys Leu Gly Gln Val Met Gly Glu Glu Asp Ser Ala Leu Gly
100 105 110

Arg Thr Gly Pro Thr Leu Ala Leu Lys Arg Tyr Phe Gln Gly Ile His
115 120 125

Val Tyr Leu Lys Glu Lys Gly Tyr Ser Asp Cys Ala Trp Glu Thr Val
130 135 140

Arg Leu Glu Ile Met Arg Ser Phe Ser Ser Leu Ile Ser Leu Gln Glu
145 150 155 160

Arg Leu Arg Met Met Asp Gly Asp Leu Ser Ser Pro
165 170

(2) IFNORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 172 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: HuIFNtau Group I core sequence (HuIFNtauGRI).

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 20
(D) OTHER IFNORMATION: /note= "where Xaa is Glu or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 146
(D) OTHER IFNORMATION: /note= "where Xaa is Leu or Val"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

```
Cys Asp Leu Ser Gln Asn His Val Leu Val Gly Arg Lys Asn Leu Arg
 1               5                  10                  15

Leu Leu Asp Xaa Met Arg Arg Leu Ser Pro Arg Phe Cys Leu Gln Asp
            20                  25                  30

Arg Lys Asp Phe Ala Leu Pro Gln Glu Met Val Glu Gly Gly Gln Leu
        35                  40                  45

Gln Glu Ala Gln Ala Ile Ser Val Leu His Glu Met Leu Gln Gln Ser
    50                  55                  60

Phe Asn Leu Phe His Thr Glu His Ser Ser Ala Ala Trp Asp Thr Thr
65                  70                  75                  80

Leu Leu Glu Gln Leu Arg Thr Gly Leu His Gln Gln Leu Asp Asn Leu
                85                  90                  95

Asp Ala Cys Leu Gly Gln Val Met Gly Glu Glu Asp Ser Ala Leu Gly
            100                 105                 110

Arg Thr Gly Pro Thr Leu Ala Leu Lys Arg Tyr Phe Gln Gly Ile His
        115                 120                 125

Val Tyr Leu Lys Glu Lys Gly Tyr Ser Asp Cys Ala Trp Glu Thr Val
    130                 135                 140

Arg Xaa Glu Ile Met Arg Ser Phe Ser Ser Leu Ile Ser Leu Gln Glu
145                 150                 155                 160

Arg Leu Arg Met Met Asp Gly Asp Leu Ser Ser Pro
                165                 170
```

(2) IFNORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 172 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: HuIFNtau Group II core

sequence (HuIFNtauGRII).

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 122
(D) OTHER IFNORMATION: /note= "where Xaa is Arg or Thr"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

Cys Asp Leu Ser Gln Asn His Val Leu Val Gly Ser Gln Asn Leu Arg
1 5 10 15

Leu Leu Gly Gln Met Arg Arg Leu Ser Leu Arg Phe Cys Leu Gln Asp
20 25 30

Arg Lys Asp Phe Ala Phe Pro Gln Glu Met Val Glu Gly Gly Gln Leu
35 40 45

Gln Glu Ala Gln Ala Ile Ser Val Leu His Glu Met Leu Gln Gln Ser
50 55 60

Phe Asn Leu Phe His Thr Glu His Ser Ser Ala Ala Trp Asp Thr Thr
65 70 75 80

Leu Leu Glu Gln Leu Arg Thr Gly Leu His Gln Gln Leu Asp Asp Leu
85 90 95

Asp Ala Cys Leu Gly Gln Val Thr Gly Glu Glu Asp Ser Ala Leu Gly
100 105 110

Arg Thr Gly Pro Thr Leu Ala Met Lys Xaa Tyr Phe Gln Gly Ile His
115 120 125

Val Tyr Leu Lys Glu Lys Gly Tyr Ser Asp Cys Ala Trp Glu Ile Val
130 135 140

Arg Leu Glu Ile Met Arg Ser Leu Ser Ser Ser Thr Ser Leu His Lys
145 150 155 160

Arg Leu Arg Met Met Asp Gly Asp Leu Ser Ser Pro
165 170

(2) IFNORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 99 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: HuIFNtau Group III core sequence (HuIFNtauGRIII).

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 7
(D) OTHER IFNORMATION: /note= "where Xaa is Gly or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 9
(D) OTHER IFNORMATION: /note= "where Xaa is Leu or Phe"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 20
(D) OTHER IFNORMATION: /note= "where Xaa is Lys or Glu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 31
(D) OTHER IFNORMATION: /note= "where Xaa is Thr or Lys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 47
(D) OTHER IFNORMATION: /note= "where Xaa is Arg or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 64
(D) OTHER IFNORMATION: /note= "where Xaa is Val or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 90
(D) OTHER IFNORMATION: /note= "where Xaa is Ile or Val"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Gln Glu Met Val Glu Gly Xaa Gln Xaa Gln Glu Ala Gln Ala Ile Ser
1 5 10 15

Val Leu His Xaa Met Leu Gln Gln Ser Phe Asn Leu Phe His Xaa Glu
20 25 30

Arg Ser Ser Ala Ala Trp Asp Thr Thr Leu Leu Glu Gln Leu Xaa Thr
35 40 45

Gly Leu His Gln Gln Leu Asp Asp Leu Asp Ala Cys Leu Gly Gln Xaa
50 55 60

Thr Gly Glu Glu Asp Ser Ala Leu Gly Arg Thr Gly Pro Thr Leu Ala
65 70 75 80

Val Lys Ser Tyr Phe Gln Gly Ile His Xaa Tyr Leu Gln Glu Lys Gly
85 90 95

Tyr Ser Asp

(2) IFNORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 172 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: HuIFNtau core sequence (HuIFNtauCS).

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 12
(D) OTHER IFNORMATION: /note= "where Xaa is Arg or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 13
(D) OTHER IFNORMATION: /note= "where Xaa is Lys or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 19
(D) OTHER IFNORMATION: /note= "where Xaa is Asp or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 20
(D) OTHER IFNORMATION: /note= "where Xaa is Glu or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 26
(D) OTHER IFNORMATION: /note= "where Xaa is Pro or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 38
(D) OTHER IFNORMATION: /note= "where Xaa is Leu or Phe"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 45
(D) OTHER IFNORMATION: /note= "where Xaa is Gly or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 46
(D) OTHER IFNORMATION: /note= "where Xaa is Gly or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 48
(D) OTHER IFNORMATION: /note= "where Xaa is Leu or Phe"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 59
(D) OTHER IFNORMATION: /note= "where Xaa is Lys or Glu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 70
(D) OTHER IFNORMATION: /note= "where Xaa is Thr or Lys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 72
(D) OTHER IFNORMATION: /note= "where Xaa is Arg or His"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 86
(D) OTHER IFNORMATION: /note= "where Xaa is Arg or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 95
(D) OTHER IFNORMATION: /note= "where Xaa is Asn or Asp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site

(B) LOCATION: 103
(D) OTHER IFNORMATION: /note= "where Xaa is Val or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 104
(D) OTHER IFNORMATION: /note= "where Xaa is Met or Thr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 120
(D) OTHER IFNORMATION: /note= "where Xaa is Val, Leu or Met"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 122
(D) OTHER IFNORMATION: /note= "where Xaa is Arg, Ser or Thr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 129
(D) OTHER IFNORMATION: /note= "where Xaa is Ile or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 132
(D) OTHER IFNORMATION: /note= "where Xaa is Lys or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 143
(D) OTHER IFNORMATION: /note= "where Xaa is Ile or Thr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 146
(D) OTHER IFNORMATION: /note= "where Xaa is Leu or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 152
(D) OTHER IFNORMATION: /note= "where Xaa is Leu or Phe"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 155
(D) OTHER IFNORMATION: /note= "where Xaa is Leu or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 156
(D) OTHER IFNORMATION: /note= "where Xaa is Ile or Thr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 159
(D) OTHER IFNORMATION: /note= "where Xaa is Gln or His"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 160
(D) OTHER IFNORMATION: /note= "where Xaa is Glu or Lys"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Cys Asp Leu Ser Gln Asn His Val Leu Val Gly Xaa Xaa Asn Leu Arg
1 5 10 15

Leu Leu Xaa Xaa Met Arg Arg Leu Ser Xaa Arg Phe Cys Leu Gln Asp
20 25 30

Arg Lys Asp Phe Ala Xaa Pro Gln Glu Met Val Glu Xaa Xaa Gln Xaa
35 40 45

Gln Glu Ala Gln Ala Ile Ser Val Leu His Xaa Met Leu Gln Gln Ser
50 55 60

Phe Asn Leu Phe His Xaa Glu Xaa Ser Ser Ala Ala Trp Asp Thr Thr
65 70 75 80

Leu Leu Glu Gln Leu Xaa Thr Gly Leu His Gln Gln Leu Asp Xaa Leu
85 90 95

Asp Ala Cys Leu Gly Gln Xaa Xaa Gly Glu Glu Asp Ser Ala Leu Gly
100 105 110

Arg Thr Gly Pro Thr Leu Ala Xaa Lys Xaa Tyr Phe Gln Gly Ile His
115 120 125

Xaa Tyr Leu Xaa Glu Lys Gly Tyr Ser Asp Cys Ala Trp Glu Xaa Val
130 135 140

Arg Xaa Glu Ile Met Arg Ser Xaa Ser Ser Xaa Xaa Ser Leu Xaa Xaa
145 150 155 160

Arg Leu Arg Met Met Asp Gly Asp Leu Ser Ser Pro
165 170

IT IS CLAIMED:

1. An isolated human interferon-τ protein, wherein said protein contains a mature interferon-τ polypeptide having a sequence derived from the sequence presented as SEQ ID NO:34.

2. An isolated human interferon-τ protein of claim 1, wherein said protein contains a mature interferon-τ polypeptide having a sequence derived from the sequence presented as SEQ ID NO:31.

3. An isolated human interferon-τ protein of claim 2, wherein said mature polypeptide has the sequence presented as SEQ ID NO:30.

4. An isolated human interferon-τ protein of claim 3, where said mature polypeptide is encoded by the sequence presented as SEQ ID NO:29.

5. An isolated human interferon-τ protein of claim 2, wherein said mature polypeptide has the sequence presented as SEQ ID NO:16.

6. An isolated human interferon-τ protein of claim 5, where said mature polypeptide is encoded by the sequence presented as SEQ ID NO:15.

7. An isolated human interferon-τ protein of claim 1, wherein said protein contains a mature interferon-τ polypeptide having a sequence derived from the sequence presented as SEQ ID NO:32.

8. An isolated human interferon-τ protein of claim 7, wherein said mature polypeptide has the sequence presented as SEQ ID NO:20.

9. An isolated human interferon-τ protein of claim 8, where said mature polypeptide is encoded by the sequence presented as SEQ ID NO:19.

10. An isolated human interferon-τ protein of claim 7, wherein said protein contains a polypeptide having the sequence presented as SEQ ID NO:12.

11. An isolated human interferon-τ protein of claim 10, where said polypeptide is encoded by the sequence presented as SEQ ID NO:11.

12. An isolated human interferon-τ protein of claim 7, wherein said protein contains a polypeptide having the sequence presented as SEQ ID NO:14.

13. An isolated human interferon-τ protein of claim 12, where said polypeptide is encoded by the sequence presented as SEQ ID NO:13.

14. An isolated human interferon-τ protein of claim 1, wherein said protein contains a mature interferon-τ polypeptide having a sequence derived from the sequence presented as SEQ ID NO:33.

15. An isolated human interferon-τ protein of claim 14, wherein said protein contains a polypeptide having the sequence presented as SEQ ID NO:8.

16. An isolated human interferon-τ protein of claim 15, where said polypeptide is encoded by the sequence presented as SEQ ID NO:7.

17. An isolated human interferon-τ protein of claim 14, wherein said protein contains a polypeptide having the sequence presented as SEQ ID NO:10.

18. An isolated human interferon-τ protein of claim 17, where said polypeptide is encoded by the sequence presented as SEQ ID NO:9.

19. An isolated human interferon-τ protein, wherein said protein contains a polypeptide having the sequence presented as SEQ ID NO:8.

20. An isolated human interferon-τ protein, wherein said protein contains a polypeptide having the sequence presented as SEQ ID NO:10.

21. An isolated human interferon-τ protein, wherein said protein contains a polypeptide having the sequence presented as SEQ ID NO:12.

22. An isolated human interferon-τ protein, wherein said protein contains a polypeptide having the sequence presented as SEQ ID NO:14.

23. An isolated human interferon-τ protein of any of claims 1 to 22, where said polypeptide further includes a leader sequence.

24. An isolated human interferon-τ protein of any of claims 1 to 23, where said protein is recombinantly produced.

25. An expression vector comprising

(a) a nucleic acid containing an open reading frame that encodes a human interferon-τ of any of claims 1 to 22; and

(b) regulatory sequences effective to express said open reading frame in a host cell.

26. A method of recombinantly producing human interferon-τ, comprising

introducing into suitable host cells, an expression vector of claim 25, where the vector contains an open reading frame (ORF) having a polynucleotide sequence which encodes a human interferon-τ polypeptide, where the vector is designed to express the ORF in said host, and

culturing said host under conditions resulting in the expression of the ORF sequence.

27. A method of inhibiting tumor cell growth, comprising

contacting the cells with a human τ-interferon of any of claims 1 to 22, at a concentration effective to inhibit growth of the tumor cells.

28. A method of claim 27, wherein said cells are human carcinoma cells, human leukemia cells, human T-lymphoma cells, and human melanoma cells.

29. A method of claim 27, wherein said cells are steroid-sensitive tumor cells.

30. A method of claim 29, wherein said cells are mammary tumor cells.

31. A method of inhibiting viral replication, comprising

contacting cells infected with a virus with a human τ-interferon of any of claims 1 to 15, at a concentration effective to inhibit viral replication within said cells.

32. A method of claim 31, where said virus is an RNA virus.

33. A method of claim 32, where said virus is human immunodeficiency virus or hepatitis c virus.

34. A method of claim 31, where said virus is a DNA virus.

35. A method of claim 34, where said virus is hepatitis B virus.

36. A method of enhancing fertility in a female mammal, comprising administering to said mammal an effective mammalian fertility enhancing amount of a human interferon-τ of any of claims 1 to 22, in a pharmaceutically acceptable carrier.

```
1                                                                    80
CTGAGATGGGATCAGAGAACCTACCTGAAGGTTCCCCCTGACCCCATCTCAGCCAGCCCAGCAGCAGCCGCATCTTCCCC

81                                                                  140
ATG GCC TTC GTG CTC TCT CTA CTG ATG GCC CTG GTG CTG GTC AGC TAT GGC CCA GGA GGA
 S1                                                                 S20
Met Ala Phe Val Leu Ser Leu Leu Met Ala Leu Val Leu Val Ser Tyr Gly Pro Gly Gly
141                                                                 200
TCT CTG GGT TGT TAC CTA TCT CGG AAA CTC ATG CTG GAT GCC AGG GAG AAC CTC AAG CTC
S21          1                                                      17
Ser Leu Gly Cys Tyr Leu Ser Arg Lys Leu Met Leu Asp Ala Arg Glu Asn Leu Lys Leu
201                                                                 260
CTG GAC CGA ATG AAC AGA CTC TCC CCT CAT TCC TGT CTG CAG GAC AGA AAA GAC TTT GGT
 18                                                                 37
Leu Asp Arg Met Asn Arg Leu Ser Pro His Ser Cys Leu Gln Asp Arg Lys Asp Phe Gly
261                                                                 320
CTT CCC CAG GAG ATG GTG GAG GGC GAC CAG CTC CAG AAG GAC CAG GCC TTC CCT GTG CTC
 38                                                                 57
Leu Pro Gln Glu Met Val Glu Gly Asp Gln Leu Gln Lys Asp Gln Ala Phe Pro Val Leu
321                                                                 380
TAC GAG ATG CTC CAG CAG AGC TTC AAC CTC TTC TAC ACA GAG CAC TCC TCT GCT GCC TGG
 58                                                                 77
Tyr Glu Met Leu Gln Gln Ser Phe Asn Leu Phe Tyr Thr Glu His Ser Ser Ala Ala Trp
381                                                                 440
GAC ACC ACC CTC CTG GAG CAG CTC TGC ACT GGA CTC CAA CAG CAG CTG GAC CAC CTG GAC
 78                                                                 97
Asp Thr Thr Leu Leu Glu Gln Leu Cys Thr Gly Leu Gln Gln Gln Leu Asp His Leu Asp
441                                                                 500
ACC TGC AGG GGT CAA GTG ATG GGA GAG GAA GAC TCT GAA CTG GGT AAC ATG GAC CCC ATT
 98                                                                 117
Thr Cys Arg Gly Gln Val Met Gly Glu Glu Asp Ser Glu Leu Gly Asn Met Asp Pro Ile
501                                                                 560
GTG ACC GTG AAG AAG TAC TTC CAG GGC ATC TAT GAC TAC CTG CAA GAG AAG GGA TAC AGC
118                                                                 137
Val Thr Val Lys Lys Tyr Phe Gln Gly Ile Tyr Asp Tyr Leu Gln Glu Lys Gly Tyr Ser
561                                                                 620
GAC TGC GCC TGG GAA ATC GTC AGA GTC GAG ATG ATG AGA GCC CTC ACT GTA TCA ACC ACC
138                                                                 157
Asp Cys Ala Trp Glu Ile Val Arg Val Glu Met Met Arg Ala Leu Thr Val Ser Thr Thr
                                                   666
621                                                                 
TTG CAA AAA AGG TTA ACA AAG ATG GGT GGA GAT CTG AAC TCA CCT TGA TGACTCTTGCCGACTA
158                                                 172
Leu Gln Lys Arg Leu Thr Lys Met Gly Gly Asp Leu Asn Ser Pro
                                                                    764
AGATGCCACATCAGCCTCCTACACCCGCCTGTGTTCATTTCAGAAGACTCTGATTTCTGCTCCAGCCACCAAATTCATTG

                                                                    844
AATTACTTTAGCTGATACTTTGTCAGTAGTAAAAAGCAAGTAGATATAAAAGTATTCAGCTGTAGGGGCATGAGTCCTGA

                                                                    924
AATGATGCCTTCCCTGATGTTATCTGTTGCTGATTTATTTATACCTTCTAGCATTTAACATACTTAAAATATTAGGAAAT

                                                   972
TTGTTAAGTTACATTTACATCTGTACATCATATTAAAATTTCTAAAACAAAAAAAAAA
```

Fig. 1

```
                -23                                                    -9
                met ala phe val leu ser leu leu met ala leu val leu val ser
oIFNτ      cccc ATG GCC TTC GTG CTC TCT CTA CTG ATG GCC CTG GTG CTG GTC AGC
huIFNτ1    cccc ATG GCC TTC GTG CTC TCT CTA CTC ATG GCC CTG GTG CTG GTC AGC

-8                          -1 +1                                      11
tyr gly pro gly gly ser leu gly cys tyr leu ser arg lys leu met leu asp ala
TAT GGC CCA GGA GGA TCT CTG GGT TGT TAC CTA TCT CGG AAA CTC ATG CTG GAT GCC
TAC GGC CCA GGA GGA TCC CTG GGT TGT GAC CTG TCT CAG AAC CAC GTG CTG GTT GGC
                                  asp         gln asn his val      val gly

 12                                                                    30
arg glu asn leu lys leu leu asp arg met asn arg leu ser pro his ser cys leu
AGG GAG AAC CTC AAG CTC CTG GAC CGA ATG AAC AGA CTC TCC CCT CAT TCC TGT CTG
AGG AAG AAC CTC AGG CTC CTG GAC GAA ATG AGG AGA CTC TCC CCT CGC TTT TGT CTG
    lys         arg             glu     arg                 arg phe

31                                                                    49
gln asp arg lys asp phe gly leu pro gln glu met val glu gly arg gln leu gln
CAG GAC AGA AAA GAC TTT GGT CTT CCC CAG GAG ATG GTG GAG GGC GAC CAG CTC CAG
CAG GAC AGA AAA GAC TTC GCT TTA CCC CAG GAA ATG GTG GAG GGC GGC CAG CTC CAG
                    ala                                 gly

50                                                                    68
lys asp gln ala phe pro val leu tyr glu met leu gln gln ser phe asn leu phe
AAG GAC CAG GCC TTC CCT GTG CTC TAC GAG ATG CTC CAG CAG AGC TTC AAC CTC TTC
GAG GCC CAG GCC ATC TCT GTG CTC CAT GAG ATG CTC CAG CAG AGC TTC AAC CTC TTC
glu ala         ile ser         his

69                                                                    87
tyr thr glu his ser ser ala ala trp asp thr thr leu leu glu gln leu cys thr
TAC ACA GAG CAC TCC TCT GCT GCC TGG GAC ACC ACC CTC CTG GAG CAG CTC TGC ACT
CAC ACA GAG CAC TCC TCT GCT GCC TGG GAC ACC ACC CTC CTG GAG CAG CTC CGC ACT
his                                                             arg

88                                                                   106
gly leu gln gln gln leu asp his leu asp thr cys arg gly gln val met gly glu
GGA CTC CAA CAG CAG CTG GAC CAC CTG GAC ACC TGC AGG GGT CAA GTG ATG GGA GAG
GGA CTC CAT CAG CAG CTG GAC AAC CTG GAT GCC TGC CTG GGG CAG GTG ATG GGA GAG
       his                  asn         ala     leu

107                                                                  125
glu asp ser glu leu gly asn met asp pro ile val thr val lys lys tyr phe gln
GAA GAC TCT GAA CTG GGT AAC ATG GAC CCC ATT GTG ACC GTG AAG AAG TAC TTC CAG
GAA GAC TCT GCC CTG GGA AGG ACG GGC CCC ACC CTG GCT CTG AAG AGG TAC TTC CAG
           ala         arg thr gly     thr leu ala leu     arg

126                                                                  144
gly ile tyr asp tyr leu gln glu lys gly tyr ser asp cys ala trp glu ile val
GGC ATC TAT GAC TAC CTG CAA GAG AAG GGA TAC AGC GAC TGC GCC TGG GAA ATC GTC
GGC ATC CAT GTC TAC CTG AAA GAG AAG GGA TAC AGC GAC TGC GCC TGG GAA ACC GTC
       his val         lys                                         thr

145                                                                  163
arg val glu met met arg ala leu thr val ser thr thr leu gln lys arg leu thr
AGA GTC GAG ATG ATG AGA GCC CTC ACT GTA TCA ACC ACC TTG CAA AAA AGG TTA ACA
AGA CTG GAA ATC ATG AGA TCC TTC TCT TCA TTA ATC AGC TTG CAA GAA AGG TTA AGA
    leu     ile         ser phe ser ser leu ile ser         glu         arg

164                                 172
lys met gly gly asp leu asn ser pro end
AAG ATG GGT GGA GAT CTG AAC TCA CCT TGA
ATG ATG GAT GGA GAC CTG AGC TCA CCT TGA
met     asp           ser
```

Fig. 2

```
                -23                                                      -9
                Met ala phe val leu ser leu leu met ala leu val leu val ser
oINFt           ATG GCC TTC GTG CTC TCT CTA CTG ATG GCC CTG GTG CTG GTC AGC
HuIFNt1                                      c
HuIFNt2                                      c
HuIFNt3                                      c

-8                                -1  +1                                 11
tyr gly pro gly gly ser leu gly cys tyr leu ser arg lys leu met leu asp ala
TAT GGC CCA GGA GGA TCT CTG GGT TGT TAC CTA TCT CGG AAA CTC ATG CTG GAT GCC
  c                   c             G    g      A    C  A  G        T   G
  c                   c         (---)G    g      A    C  A  G        T   G
  c       g           c      C G    G    g      A    C  A  G        T   G

12                                    20                                 30
arg glu asn leu lys leu leu asp arg met asn arg leu ser pro his ser cys leu
AGG GAG AAC CTC AAG CTC CTG GAC CGA ATG AAC AGA CTC TCC CCT CAT TCC TGT CTG
    A           G                GA       GG                   GC  TT
    A           G                 A       GG                   GC  TT
  C C           G             G   A       GG              T    GC  T

31                                        40                             49
gln asp arg lys asp phe gly leu pro gln glu met val glu gly asp gln leu gln
CAG GAC AGA AAA GAC TTT GGT CTT CCC CAG GAG ATG GTG GAG GGC GAC CAG CTC CAG
                    c  C  t a          a                  G
                    c  C  t a      TAG a                  G
                    c  C  t C                           t  G
HuIFNt4                           !                     t  G
HuIFNt5                           !                     t  G
HuIFNt6                           !                        G
HuIFNt7                           !                     T  AG      T

50                                            60                         68
lys asp gln ala phe pro val leu tyr glu met leu gln gln ser phe asn leu phe
AAG GAC CAG GCC TTC CCT GTG CTC TAC GAG ATG CTC CAG CAG AGC TTC AAC CTC TTC
G   C         A   T          C T
G   C         A   T          C T
G   C         A   T          C
G   C         A   T          C
G   C         A   T          C
G   C         A    T         C   A
G   C         A T T          C T

69                                                80                     87
tyr thr glu his ser ser ala ala try asp thr thr leu leu glu gln leu cys thr
TAC ACA GAG CAC TCC TCT GCT GCC TGG GAC ACC ACC CTC CTG GAG CAG CTC TGC ACT
C                                                                      C
C                                                                      C
C                                                                      C
C                                                                      C
C                                                                      C
C           G                                                          C
C   A       G                          t                               CT
```

Fig. 3A

```
88       90                                                  100                 106
gly leu gln gln gln leu asp his leu asp thr cys arg gly gln val met gly glu
GGA CTC CAA CAG CAG CTG GAC CAC CTG GAC ACC TGC AGG GGT CAA GTG ATG GGA GAG
          T                 A         t G       CT    g   g
          T                 A         t G       CT    g   g
          T               t G         t G       CT    g   g       C
          T               t G         t G       CT    g   g       C
          T               t G         t G       CT    g   g       C
          T               t G           G       CT    g   g       C
          T               t G         t G     t CT    g   g T     CT

107        110                                                 120                 125
glu asp ser glu leu gly asn met asp pro ile val thr val lys lys tyr phe gln
GAA GAC TCT GAA CTG GGT AAC ATG GAC CCC ATT GTG ACC GTG AAG AAG TAC TTC CAG
            CC       a  GG  C   G       CC C   G T C         G
            CC       a  GG  C   G       CC C   G T C         G
            CC       a  GA  C   G       CC C   G   A         G     t
            CC       a  GG  C   G       CC C   G   A         C     t
            CC       a  GG  C   G       CC C   G   A         C     t
            CC       a  GG  C   G       CC C   G             GC
            CC       a  GG  C   G       CC C   G             GC

126              130                                                 140         144
gly ile tyr asp tyr leu gln glu lys gly tyr ser asp cys ala trp glu ile val
GGC ATC TAT GAC TAC CTG CAA GAG AAG GGA TAC AGC GAC TGC GCC TGG GAA ATC GTC
        C    T         A                                                 C
        C    T         A                                                 C
        C    T         A                   t   t                           t
        C    T         A                   t   t                   !
        C    T         A                   t   !
        C   AT                                       !
        C    T                       !

145                  150                                                 160         163
arg val glu met met arg ala leu thr val ser thr thr leu gln lys arg leu thr
AGA GTC GAG ATG ATG AGA GCC CTC ACT GTA TCA ACC ACC TTG CAA AAA AGG TTA ACA
    C G   a   C         T   T   T   TC   T   T   G         G             G
      g   a   C         T   T   T   TC   T   T   G         G             G
    C G   a   C         T   t g T   TC         G       C                 G

164                          172
lys met gly gly asp leu asn ser pro
AAG ATG GGT GGA GAT CTG AAC TCA CCT TGA
 T       A       c     G
 T       A       c     G
 T       A       c     G
```

Fig. 3B

```
                -23                                                    -9
oTP-1           Met ala phe val leu ser leu leu met ala leu val leu val ser
HuIFNτ1
HuIFNτ2
HuIFNτ3

-8                          -1  +1                                     11
tyr gly pro gly gly ser leu gly cys tyr leu ser arg lys leu met leu asp ala
                              asp       gln asn his val     val gly
                          (---)asp      gln asn his val     val gly
                            arg  asp      gln asn his val     val gly

12                              20                                     30
arg glu asn leu lys leu leu asp arg met asn arg leu ser pro his ser cys leu
    lys         arg             glu   arg                 arg phe
    lys         arg             gln   arg                 arg phe
ser gln         arg         gly gln   arg           leu arg phe

31                                  40                                 49
gln asp arg lys asp phe gly leu pro gln glu met val glu gly asp gln leu gln
                        ala                             gly
                        ala       (Stop)                gly
                        ala phe                         gly
HuIFNτ4                         !                       gly
HuIFNτ5                         !                       gly
HuIFNτ6                         !                       gly
HuIFNτ7                         !                   val ser     phe

50                                      60                             68
lys asp gln ala phe pro val leu tyr glu met leu gln gln ser phe asn leu phe
glu ala         ile ser         his
glu ala         ile ser         his
glu ala         ile ser         his
glu ala         ile ser         his
glu ala         ile ser         his
glu ala         ile ser         his lys
glu ala         ile ser         his

69                                          80                         87
tyr thr glu his ser ser ala ala trp asp thr thr leu leu glu gln leu cys thr
his                                                                arg
his                                                                arg
his                                                                arg
his                                                                arg
his                                                                arg
his         arg                                                    leu
his lys     arg
```

Fig. 4A

```
88       90                                                  100                 106
gly leu gln gln gln leu asp his leu asp thr cys arg gly gln val met gly glu
        his                 asn         ala     leu
        his                 asn         ala     leu
        his                 asp         ala     leu             thr
        his                 asp         ala     leu             thr
        his                 asp         ala     leu             thr
        his                 asp         ala     leu             thr
        his                 asp         ala     leu         leu thr

107         110                                                 120                 125
glu asp ser glu leu gly asn met asp pro ile val thr val lys lys tyr phe gln
            ala         arg thr gly     thr leu ala leu     arg
            ala         arg thr gly     thr leu ala leu     arg
            ala         arg thr gly     thr leu ala met     arg
            ala         arg thr gly     thr leu ala met     thr
            ala         arg thr gly     thr leu ala met     thr
            ala         arg thr gly     thr leu ala         ser
            ala         arg thr gly     thr leu ala         ser

126             130                                                 140             144
gly ile tyr asp tyr leu gln glu lys gly tyr ser asp cys ala trp glu ile val
        his val         lys                                             thr
        his val         lys                                             thr
        his val         lys
        his val         lys                                         !
        his val         lys                 !
        his ile                                         !
        his val                     !

145                 150                                                 160         163
arg val glu met met arg ala leu thr val ser thr thr leu gln lys arg leu thr
    leu     ile         ser phe ser ser leu ile ser         glu         arg
            ile         ser phe ser ser leu ile ser         glu         arg
    leu     ile         ser     ser ser         ser     his             arg

164                             172
lys met gly gly asp leu asn ser pro stop
met     asp             ser     stop
met     asp             ser     stop
met     asp             ser     stop
```

Fig. 4B

INTERNATIONAL SEARCH REPORT

In· onal Application No
PCT/US 96/06911

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/20 C07K14/555 A61K38/21

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,94 10313 (UNIVERSITY OF FLORIDA) 11 May 1994 cited in the application see sequences n0 3, 4, 11 and 12 see page 8, line 12 - page 9 see claims; examples 5-7 ---	1,3, 23-36
A	JOURNAL OF BIOLOGICAL CHEMISTRY (MICROFILMS), vol. 269, no. 14, 8 April 1994, MD US, pages 10864-10868, XP002010875 A.E. WHALEY ET AL: "Identification and cellular localization of unique interferon mRNA from human placenta" see the whole document --- -/--	1,3, 31-33

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 August 1996	28.08.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Le Cornec, N

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/06911

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NATURE, vol. 330, 26 November 1987, LONDON GB, pages 377-379, XP002010876 K.IMAKAWA ET AL: "Interferon like sequence of ovine trophoblast protein secreted by embryonic trophectoderm" cited in the application see the whole document -----	1

1

INTERNATIONAL SEARCH REPORT

:national application No.
PCT/US 96/06911

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Please see Further Information sheet enclosed.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US96/06911

FURTHER INF RMATION CONTINUED FROM PCT/ISA/210

Remark : Although claims 27-35 (as far as they do not concern in vivo methods) and claim 36 are related to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In··· ·ional Application No
PCT/US 96/06911

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9410313	11-05-94	AU-B-	5444994	24-05-94
		CN-A-	1090510	10-08-94
		EP-A-	0669981	06-09-95
		JP-T-	8505047	04-06-96